ARTERIAL REPLACEMENT AND RECONSTRUCTION

A Five-year Review

DAVID J. TIBBS
M.C., M.S. Lond., F.R.C.S.
READER IN SURGERY, UNIVERSITY OF DURHAM; HONORARY CONSULTANT SURGEON, ROYAL VICTORIA INFIRMARY, NEWCASTLE UPON TYNE

METHODS of arterial replacement and reconstruction have passed the stage of enthusiastic but sometimes ill-judged usage and are now being critically appraised. Sufficient experience has been gained to predict the likely outcome of any procedure over the ensuing year or two; and soon unsatisfactory results will be due to bad selection of patient or procedure or both.

This paper describes five years' experience of these methods in the professorial surgical unit of the Royal Victoria Infirmary. The review covers the *total* experience with arterial replacement and reconstruction during that time except that repairs of recent arterial injuries and embolectomies are excluded since these have been reviewed elsewhere (Hardy and Tibbs 1960, Tibbs 1960). The comparatively small number of patients involved has facilitated complete follow-up. The main aim has been to determine the factors leading to success or failure in the different procedures.

In the past five years, planned gradual development of arterial surgery has taken place in this unit. In the first three years homografts were employed almost exclusively; in the past two years woven or knitted crimped 'Dacron' ('Terylene') prostheses have been used for all arterial replacements, but recently thromboendarterectomy has been performed with increasing frequency for arterial reconstruction, particularly of major abdominal arteries.

Table I shows the disorders in the 116 patients in this series.

Materials for Arterial Replacement

Between 1955 and 1958 the arterial homografts used for arterial replacement were prepared by immersion for 48 hours in an antibiotic solution (Fisher et al. 1956), freeze-dried (Eastcott et al. 1954), and stored in evacuated tubes (Flewett et al. 1955). This process was very convenient and ensured adequate sterilisation.

Table II summarises the main complications attributable to the homograft. Of 40 homografts no less than 5 gave way. In each case there was evidence that the graft had leaked or ruptured where graft substance was sutured to graft substance—for example, where a suture line repaired a defect in the homograft. This weakness is understandable since the freeze-dried graft is dead tissue and a suture line within it is not bridged by living tissue for many months; it is only ensheathed, and this may provide inadequate support.

Many homografts closed off and specimens could be obtained occasionally at a further operation or, in 1 patient who died from a different condition, at necropsy. In the homografts that had closed a thick deposit of fibrinous material, indistinguishable from atherosclerosis, overlay the original intimal layer; and this accords with Duguid's theory of the development of atherosclerosis (Duguid 1946, 1948, 1955). In the first two years this was the only process observed, but later two homografts removed after functioning for four years both showed gross atheromatous change—i.e., thick yellow areas of fatty deposits with deformity and narrowing of the grafted artery; microscopically the graft showed extensive vascularisation with hæmorrhages under existing plaques, again supporting Duguid's (1960) beliefs.

Our experience, therefore, like that of other workers, showed that the homograft tended to be weak at points where it was sutured to itself and that it was liable to participate actively in the progress of atherosclerosis (Szilagyi et al. 1957). We doubt whether any method of preparing the homograft is immune from these changes.

TABLE I—CONDITIONS FOR WHICH ARTERIAL RECONSTRUCTION OR REPLACEMENT WAS UNDERTAKEN IN 116 CASES

Condition	No. of cases
Abdominal aortic aneurysms	24
Occlusion of abdominal aorta and/or iliac arteries	33
Occlusion of lower-limb arteries	45
Miscellaneous:	
Aneurysm—	
Subclavian (cervical rib)	1
Femoral	5
Popliteal	1
Traumatic arteriovenous fistula	1
Internal-carotid-artery narrowing	5
Renal-artery narrowing	1
Total	116

TABLE II—COMPLICATIONS DUE TO ARTERIAL "GRAFT" ITSELF

Material	Total no. of grafts	Time of onset of complication	Complication	Outcome
Homograft	40	3rd day	Leakage from suture line in graft (femoral)	Repaired successfully
		1st week	Leakage from suture line in graft (femoral)	Graft replaced successfully
		2nd mo.	Aneurysm around graft (iliac)—early in series	Replaced; further leakage, ileus; death
		8th mo.	Leakage into duodenum from sutured defect in graft (aortic)	Repair; but embolus dislodged from thoracoabdominal aneurysm, mesenteric infarction; death
		11th mo.	Leakage from graft (femoropopliteal)	Repair; but thrombosis of graft; amputation (indicated originally but postponed by graft)
Orlon	2	5th mo.	Abscess around abdominal prosthesis (aortic)	Drained; leakage from suture line; repaired; leakage from another suture line; death
Dacron	50	2nd mo.	Staphylococcal infection of bifurcated aorto-iliac prosthesis (Leriche syndrome)	Prosthesis removed; patient reverted to "pre-graft" state
		5th mo.	Rejection of prosthesis from outset, recurrent massive effusion which ceased immediately prosthesis removed (femoropopliteal)	Prosthesis removed; limb survived

These observations, combined with the obvious difficulties of collecting homografts from cadavers, led to our abandoning this form of arterial replacement, and we now avoid the homograft, since it lacks durability.

Fortunately other means of arterial replacement were available. The advantages of the crimped woven or knitted dacron arterial prosthesis had already been demonstrated (Crawford et al. 1958, Julian et al. 1959); and from 1958 these arterial substitutes were routinely used by us whenever an artery had to be replaced or bypassed. (Two 'Orlon' bifurcated aortic prostheses were used in 1956.) We have found the change beneficial; no case of leakage or rupture of the prosthesis or its anastomosis to the patient's arteries has occurred (table II). Leakage through the material of the prosthesis at the time of insertion has not proved a problem because a routine was early established of anastomosing the upper end of the prosthesis to the patient's artery and allowing short bursts of arterial blood to flow into the prosthesis until it was entirely leak-proof; alternatively, the effectiveness of preclotting was tested by introducing blood from a syringe under pressure into the prosthesis. Infection, although uncommon, has been the most alarming complication with the orlon and dacron prostheses (see table II). In 1 patient, sterile fluid leaked for two months from a sinus overlying the prosthesis before breakdown of an anastomosis necessitated its removal. This may have been due to host rejection of the plastic material rather than sepsis; the prosthesis had been washed in cetrimide—a practice to be avoided. Sepsis is dangerous to any arterial "graft"; and our experience is not an argument against plastic prostheses, but rather a reason for not inserting any foreign material if the patient's own arteries can be reconstructed. This is one reason why in the abdominal arteries thromboendarterectomy is preferable to arterial replacement.

Late occlusion was not more frequent in the crimped dacron prosthesis than in the homograft, and in those cases where a specimen of the dacron prosthesis was obtained after its closure the plastic tube showed thick deposits of atherosclerotic material on its inner aspect. The gross atheromatous changes observed in homografts after four years have not yet been encountered, and the immunity of the dacron prosthesis to late vascularisation in its wall may protect it from the severe late degenerative changes which occurred in homografts. But until effective methods of controlling atherosclerosis are developed, no "graft" or reconstruction can escape narrowing by the fibrinous deposit characteristic of the disease. The difference between the thick opaque pseudo-intimal layer formed inside a dacron arterial prosthesis in the atherosclerotic patient and the transparent pseudo-intima of a prosthesis in the healthy animal is striking.

We have frequently observed that the dacron prosthesis adheres only lightly to its surrounding fibrous sheath and to its pseudo-intima, both shortly after insertion and later. The dacron tube is not intimately incorporated in the tissue and acts merely as a conduit lined by cells laid down by the blood-stream and by ingrowth from each end. The strength of the new vessel depends entirely on the fabric of the prosthesis, and how long this remains unimpaired is still unknown; theoretically the easily detached internal layer seems vulnerable but we have not as yet encountered a "graft" failure which could be ascribed to its detachment.

Our general conclusion is that the crimped dacron (terylene) prosthesis (and presumably 'Teflon' as well) is to be preferred to the homograft because of its greater durability; but any form of arterial "graft" should be avoided whenever there is an acceptable and equally effective alternative.

Abdominal Aortic Aneurysm

The term "abdominal aortic aneurysm" in this paper refers to a distinct expansion of the infrarenal portion of the aorta, readily palpable through the abdominal wall; the aneurysms found at operation had diameters at least four times as great as that of the normal aorta. Prominence or tortuosity of the aorta was not considered sufficient reason for operation.

Fig. 1 shows the results obtained by treating both ruptured and unruptured abdominal aortic aneurysms by replacement with a "graft". Details of postoperative deaths are summarised in table III, which shows that resection and replacement of an unruptured aneurysm with a "graft" (dacron for preference) carried a low mortality-rate; the figures for long-term survival compare favourably with the data of Estes (1950) and Barratt-Boyes (1957) for untreated aneurysms. As regards leaking or ruptured aneurysms, the value of operation is shown by

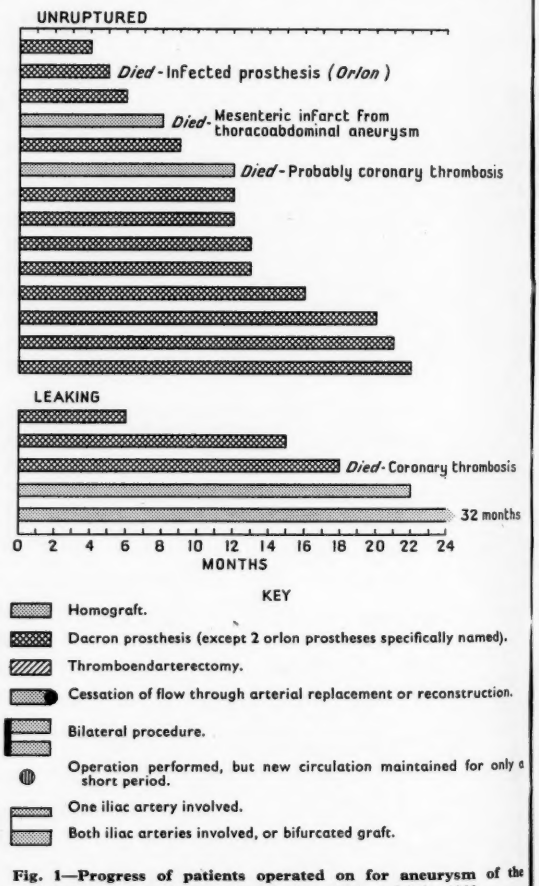

UNRUPTURED
Died - Infected prosthesis (Orlon)
Died - Mesenteric infarct from thoracoabdominal aneurysm
Died - Probably coronary thrombosis
LEAKING
Died - Coronary thrombosis
32 months
0 2 4 6 8 10 12 14 16 18 20 22 24
MONTHS
KEY
Homograft.
Dacron prosthesis (except 2 orlon prostheses specifically named).
Thromboendarterectomy.
Cessation of flow through arterial replacement or reconstruction.
Bilateral procedure.
Operation performed, but new circulation maintained for only a short period.
One iliac artery involved.
Both iliac arteries involved, or bifurcated graft.

Fig. 1—Progress of patients operated on for aneurysm of the abdominal aorta between September, 1955, and July, 1960.

In this and in the succeeding figures each bar represents one procedure and, except where indicated, 1 patient. The length of each bar corresponds to the number of months from the time of operation until July, 1960, or until the cessation of flow through the arterial replacement or reconstruction; unless termination of flow (see key) is specifically indicated, circulation through the arterial replacement or reconstruction continued actively on July 1, 1960. Patients who died in hospital postoperatively are shown in table III.

TABLE III—ANALYSIS OF DEATHS IN HOSPITAL FOLLOWING OPERATION FOR ARTERIAL REPLACEMENT OR RECONSTRUCTION

Condition for which operation performed	No. of cases	No. of deaths	Comment
Abdominal aneurysm:			
Unruptured	14	0	..
Leaking or ruptured	10	1	Cardiac arrest at start of operation for rupture of massive aneurysm; restarted; but death at conclusion of operation; recent myocardial infarct
		1	5th postop. day: broncho-pneumonia
		1	8th postop. day: pulmonary embolus
		2	2nd postop. week: renal failure
Occlusion of abdominal aorta and iliac arteries —replacement with homograft or plastic prosthesis	15 (19 ops.)	1	1 hr. postop.: coronary thrombosis
		1	24 hr. postop.: cerebral thrombosis
		1	10th postop. day: pulmonary embolus
		1	2nd postop. week: intractable ileus
Occlusion of abdominal aorta and iliac arteries —thromboendarterectomy	18	0	In 1 patient with gangrene of bilateral amputation stumps and of penis, operation was attempted but abandoned because no patent peripheral vascular bed could be found: died 10 days later
Femoropopliteal occlusion (all procedures)	45 (61 ops.)	0	

the survival of half our cases. It was noteworthy that 3 patients with ruptured aneurysms had no premonitory symptoms. We have found the operation for resection of abdominal aortic aneurysms so satisfactory that it seems justifiable to urge the patient to undergo it if the aneurysm causes pain and to recommend operation even if symptoms are slight or absent.

As regards the operative technique, we believe the most important points are: (1) avoidance of damage to the iliac veins and inferior vena cava; (2) injection of a large volume of dilute heparin into that part of the circulation which is rendered temporarily stagnant during operation; (3) excluding the presence of clot in the iliac arteries; (4) proceeding with the operation expeditiously. It is important that a patient with a ruptured aneurysm should be taken direct from the ambulance to the theatre; lengthy attempts at resuscitation should not be made elsewhere.

In several of our patients with symptoms of lower-limb ischæmia definite improvement followed removal of the aneurysm; in some, minor emboli had clearly originated from the aneurysm. In considering whether to resect an aortic aneurysm the threat to the lower-limb circulation must be taken into account. In 1 case popliteal embolism was the first manifestation of abdominal aneurysm.

In 1 patient with a leaking aneurysm, gangrene developed in a limb after operation and amputation was necessary. In retrospect, we consider that this patient, one of the earlier ones in the series, might have been spared this if, at operation, a large volume of heparin solution had been injected into the stagnant circulation, inspection for clot had been made at the end, and the operation had been speedily concluded. With greater experience of embolectomy (Tibbs 1960) we would nowadays use this procedure rather than regard it as unduly hazardous as we did in this case. Loss of a limb after resection of an aortic aneurysm is possible, but with precautions the risk seems to be small.

Occlusion of Aorta and Iliac and Common Femoral Arteries

The information provided by translumbar aortograms was an invaluable guide in operations for occlusion of the abdominal aorta and iliac and common femoral arteries. These aortograms, obtained by the methods previously described (Tibbs and Leslie 1958), caused no significant morbidity. Translumbar aortography has proved so satisfactory that the radiology department of this hospital does not intend to change over to the more fashionable method of retrograde arterial catheterisation.

In several patients in whom some form of arterial replacement or bypass procedure was carried out for the Leriche type of syndrome, the initial success was short-lived and the " graft " closed off within a few months (see fig. 2). Further operations on these occluded " grafts " showed that the original abdominal aortic disease had been more severe than the aortogram indicated, and, where occlusion had developed, the aorta was grossly diseased in the immediately vicinity of the anastomosis. Clearly this was inviting spread of atherosclerotic fibrinous occlusion from the diseased aorta into the " graft "; and, incidentally, small emboli (or at any rate blood already beginning to form thrombus) might be carried to the lower limb where they would cause or accelerate arterial occlusion. Anyone who has seen inside such aortæ cannot help being impressed by the loose debris and recent thrombus there; some of this must become detached and travel distally.

Surgery of a blocked and atheromatous aorta must be thorough. The aorta can be removed as far as the renal arteries and replaced by a " graft "; this has all the drawbacks of a " graft " already referred to, and, in addition, collaterals are sacrificed. The alternative procedure of thromboendarterectomy is very attractive. Our experience (see fig. 3) is not very extensive; but abdominal-aortic and common-iliac thromboendarterectomy through a longitudinal incision in the arterial wall has proved a straightforward procedure with a low mortality and morbidity. The results in the short period of observation have

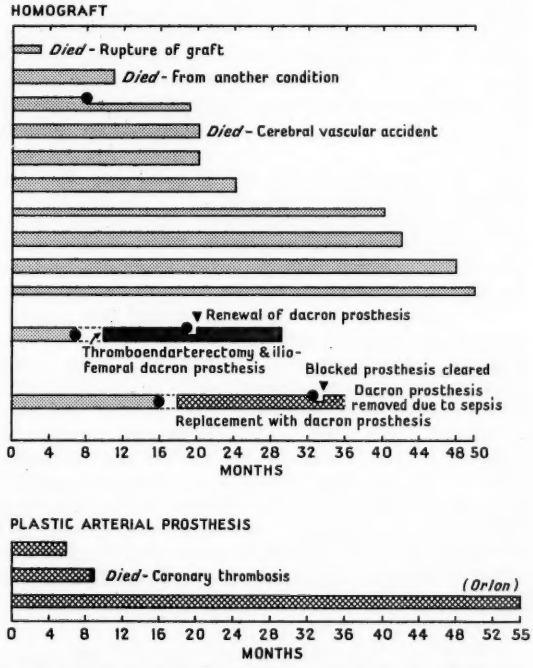

HOMOGRAFT
Died - Rupture of graft
Died - From another condition
Died - Cerebral vascular accident
Renewal of dacron prosthesis
Thromboendarterectomy & ilio-femoral dacron prosthesis
Blocked prosthesis cleared
Dacron prosthesis removed due to sepsis
Replacement with dacron prosthesis
0 4 8 12 16 20 24 28 32 36 40 44 48 50
MONTHS
PLASTIC ARTERIAL PROSTHESIS
Died - Coronary thrombosis
(Orlon)
0 4 8 12 16 20 24 28 32 36 40 44 48 52 55
MONTHS

Fig. 2—Progress of patients with occlusion of abdominal aorta and iliac arteries treated by arterial replacement in 1955–59 (for key see fig. 1).
The material used for arterial replacement is indicated.

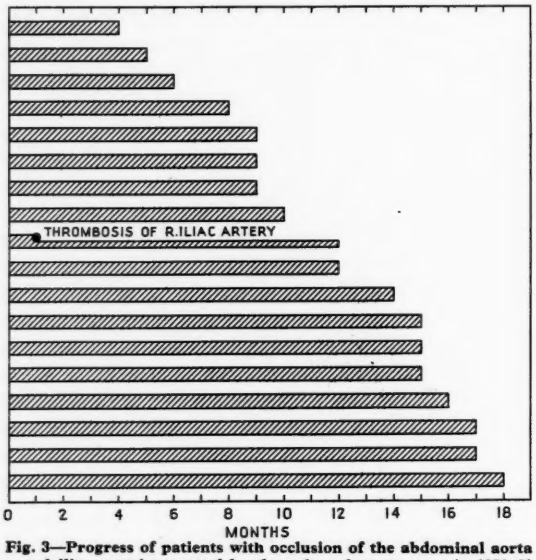


Fig. 3—Progress of patients with occlusion of the abdominal aorta and iliac arteries treated by thromboendarterectomy in 1959–60 (for key see fig. 1).

Those patients in whom operation also included thromboendarterectomy on the common femoral artery have not been separately distinguished.

been excellent. Thromboendarterectomy was extended to a point above the gross atheroma or about 1 in. below the renal arteries, whichever was the lower. Commonly the disease process did not stop at this level, and in this event the aorta was manually compressed above the pancreas and the aortic clamp released; then the upper abdominal aorta was cleared of thrombus or loose debris through the opening in the aorta, flushed with heparin solution and a spurt of the patient's own blood, and the clamp reapplied. Care was taken not to introduce any material into the renal arteries. This manœuvre, performed in about a dozen patients, appeared to provide an excellent compromise.

If there was aortographic and arteriographic evidence of significant disease in the lower-limb arterial system, a bilateral lumbar sympathectomy was performed in addition to thromboendarterectomy. This operation is not difficult to combine with the other procedure, and we consider it beneficial.

Thromboendarterectomy of the external iliac arteries, although technically more difficult, was nevertheless a practical proposition; a ring stripper (Cannon 1958) could usually be passed from the common femoral artery into the common iliac artery.

One pattern of arterial occlusion we find of particular interest: in this condition the patient has aorto-iliac occlusion or narrowing, and bilateral superficial femoral * blockage; the patency of the common femoral arteries is maintained by collateral flow through the internal and external iliac or the inferior epigastric and the profunda femoris arteries. This was observed in 8 cases. At operation the aorta and iliac arteries were reopened to restore a pulsatile circulation via the common femoral artery to the profunda femoris, and bilateral sympathectomy was carried out. These patients lost all their gluteal claudication and in 7 claudication in the calf became slight or absent; in some, good peripheral pulses were restored although, of course, the superficial femoral arteries remained shut. The presence of the extensive collaterals in the thigh necessary for this seem a feature of this particular combination of occlusions. Whatever the explanation, in aortoiliac occlusion with bilateral superficial femoral block a good result is usually obtained by restoring the circulation to the profunda femoris vessels. This needs stressing because over-extensive operations on the arterial tree can only defeat their own ends.

Although the indications for reopening completely occluded aortæ or iliac arteries are usually clear, the wisdom of performing thromboendarterectomy on patent but narrowed aortæ and iliac arteries is less certain. Narrowing at the aortic bifurcation can cause disabling claudication, although the femoral pulses may appear reasonably strong. Our group includes 7 such patients, all of whom did well and were relieved of symptoms. If the symptoms are sufficiently severe, such patients can be safely and reliably relieved by thromboendarterectomy just like those with complete aortic or iliac artery closure.

4 of our patients with occlusion of the aorta and iliac arteries had had this for five years or longer, the onset having occurred at an early age when Buerger's disease had been diagnosed. Recent deterioration brought them to the outpatient department, and it seems likely that the correct diagnosis throughout was occlusion or narrowing of the aortic bifurcation. Operation transformed all these patients' lives by removing a serious and longstanding disability, and in 2 patients who had already lost a limb imminent danger to the remaining limb was averted. In the past, aortic occlusion in young men has clearly been confused with Buerger's disease; in such cases aortography should be performed if there is doubt about the state of the aortic bifurcation.

In addition, 5 patients were seen with critically ischæmic lower limbs, and in 3 of these extensive gangrene of a limb was already present. Reopening the aorta and iliac arteries produced a dramatic change not only in the limb circulation but also in the patients' general health and well-being. Threatened gangrene of the lower extremities in the presence of disease at the aortic bifurcation can almost certainly be reversed provided there is a vascular bed into which the renewed circulation can flow: in our series this was achieved in every case but 1. Because surgery is so effective in this condition, this should be widely known so that the condition is diagnosed early and treated surgically before the damage is irretrievable.

Femoropopliteal-artery Occlusion

In most patients operated on for occlusion of the superficial femoral artery a homograft or dacron prosthesis bypass was used. The "graft" ran from the common femoral artery to either the upper or the lower part of the popliteal artery, which was exposed from the medial aspect. The patients have been divided into two groups; those with claudication alone and those with rest pain or gangrene of the toes as well (fig. 4).

Good results were obtained in the group with claudication alone, and it is reasonable to infer that in these patients the dacron bypass procedure will give a high proportion of successes which will last for a long period.

In the group with rest pain or gangrene, on the other

* The division of the femoral artery into common femoral above the profunda femoris and a superficial femoral distally is fully justified by functional and pathological considerations. It is a shortcoming of modern anatomical terminology that this distinction is not made, although in an analogous situation the terms "common carotid" and "common iliac" are used; moreover the term "arteria profunda femoris" invites such a distinction.

hand, immediate or early closure was common. In many of these patients an arterial bypass procedure was used in an attempt to avert amputation; but the majority came to amputation within a few months, often despite repeated attempts to re-establish the circulation (fig. 4). A likely explanation is that a lower limb with rest pain in the foot or with actual gangrene almost certainly has two sites of arterial occlusion, the upper being usually in the femoro-popliteal region and the lower involving one or both tibial arteries. This has repeatedly been demonstrated arteriographically. In these circumstances a bypass " graft " inserted into the popliteal artery (it is rarely practicable to anastomose to an artery at a lower level) delivers the blood it carries into a restricted and diseased arterial bed and cannot be expected to succeed for long. We have now reluctantly stopped using femoropopliteal bypass " grafts " when the patient complains of rest pain or gangrene, unless a properly timed arteriogram shows a reasonably healthy popliteal artery running into at least one good tibial artery, and even then we often consider it wise to try the other available measures, including sympathectomy, before resorting to a bypass procedure.

When threatened gangrene is due to occlusion of the limb vessels, arterial surgery is far less likely to succeed than it is when the cause lies in the abdominal arteries.

Indications, besides rest pain and gangrene, of likely failure of a bypass " graft " procedure are: (1) the appearance on the arteriogram of extensive roughening of the lower parts of the popliteal or the tibial arteries, (2) the absence at operation of the normal polished appearance of the interior of the popliteal artery, and (3) a sense of resistance when the distal vascular bed is flushed through with a syringe. All these signs were associated with a high rate of immediate or early closure of the " graft ". Often more than one of these adverse features was present in a single case. Once the popliteal artery has actually been opened it is naturally difficult to abandon the procedure, because the arteriotomy, however carefully closed, may cause thrombosis of the meagre stream of blood within. But if a roughened interior is found, and if flushing distally offers appreciable resistance, it is probably wisest to turn back and perform sympathectomy if this has not already been done, or even an amputation (if indicated). It is clearly desirable to avoid this situation, and with increased experience we now rely considerably on the arteriogram for recognising the bad proposition in which operation on the arteries should not be attempted; this is particularly important if there is no indication for immediate amputation, because any interference with the popliteal artery may reduce the circulation sufficiently to precipitate intractable rest pain.

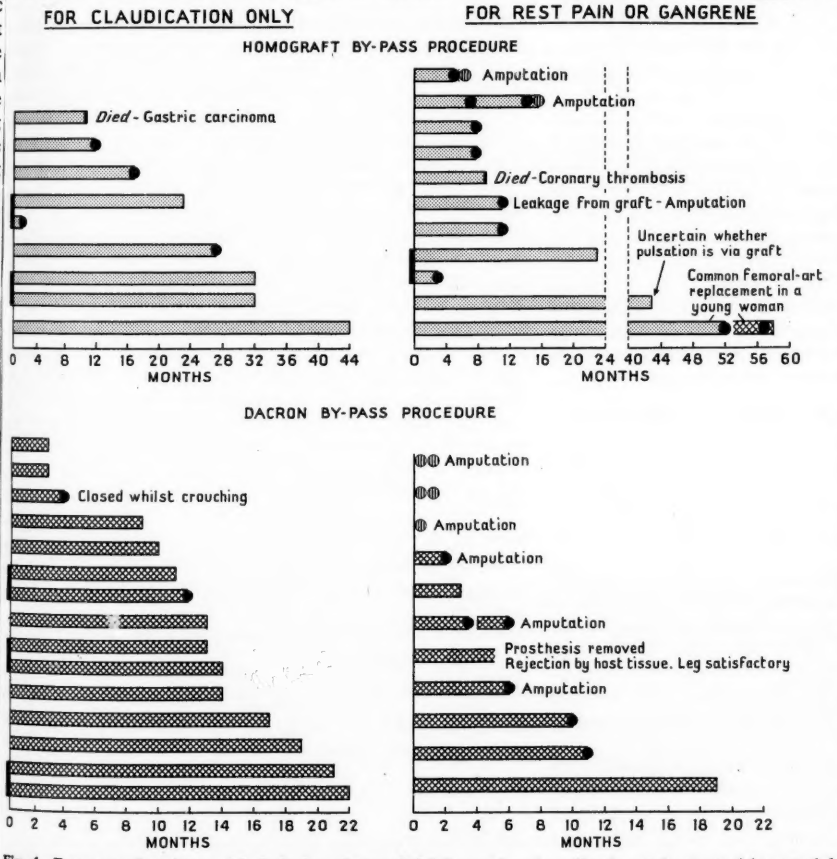

FOR CLAUDICATION ONLY
FOR REST PAIN OR GANGRENE
HOMOGRAFT BY-PASS PROCEDURE
Amputation
Amputation
Died - Gastric carcinoma
Died - Coronary thrombosis
Leakage from graft - Amputation
Uncertain whether pulsation is via graft
Common Femoral-art replacement in a young woman
0 4 8 12 16 20 24 28 32 36 40 44
MONTHS
0 4 8 12 16 20 24 40 44 48 52 56 60
MONTHS
DACRON BY-PASS PROCEDURE
Amputation
Closed whilst crouching
Amputation
Amputation
Amputation
Prosthesis removed
Rejection by host tissue. Leg satisfactory
Amputation
0 2 4 6 8 10 12 14 16 18 20 22
MONTHS
0 2 4 6 8 10 12 14 16 18 20 22
MONTHS

Fig. 4—Progress of patients with occlusion of superficial femoral and popliteal arteries treated by arterial bypass procedure in the period 1956–60 (for key see fig. 1).

The patients have been divided into two groups according to whether claudication was the only manifestation or whether, in addition, rest pain or gangrene of the toes was present. Indication is given if amputation had to be resorted to eventually. (Note the different scales employed for homografts and the more recent dacron [terylene] " grafts ".)

Thromboendarterectomy of Common and Superficial Femoral and of Popliteal Arteries

In 12 patients thromboendarterectomy of the common femoral artery was undertaken in conjunction with a femoropopliteal bypass when gross intimal thickening was apparent; and we believe that a much more satisfactory state of affairs was established in the artery adjacent to the upper end of the " graft "; the results in these patients support this conclusion.

In only 1 patient out of 6 on whom superficial-femoral-artery thromboendarterectomy was performed were the vessels still open at the end of seven months; in 3 of the cases closure occurred within a few hours and a dacron bypass " graft " was immediately substituted. Thus thromboendarterectomy in the superficial femoral artery has not given encouraging results among our few cases. In view of the

excellent results obtainable in the abdominal arteries, it seems possible that an important factor in the relatively poor results may be the use of a blind technique (i.e., a ring stripper) on the lower-limb arteries, combined with the difference in the size of the lumen. At this stage in our experience we conclude that thromboendarterectomy on common femoral arteries or arteries proximal to them has proved successful, but below this level the procedure has been disappointing; but we have recently seen the good results being obtained by Prof. C. Semb and his colleagues in Oslo and remain interested in the method.

Operative Mortality

Failures to save the lives of patients with ruptured aneurysms are not considered in this paper. Apart from the deaths already discussed to which shortcomings or infections of the material used for arterial replacement contributed, there were 4 deaths in hospital precipitated in some way by the operation (table III). 3 deaths were due to thrombotic conditions—coronary thrombosis, cerebral thrombosis, and pulmonary embolism. The patients operated on would undoubtedly be more liable to these complications; because of this, efforts were made to avoid anoxia or hypotension during operation, and all patients were urged to move their legs freely after operation to discourage venous thrombosis. These deaths occurred early in the series, and possibly the risk of these complications has been reduced; but the risk remains in any procedure on a patient with advanced vascular disease. 1 patient died of intractable ileus, the cause of which remained obscure despite re-exploration (permission for necropsy was not given). Since this episode, in abdominal procedures we have routinely delivered all the small bowel and wrapped it in moist towels; at the end of the operation it is carefully returned into an " ideal " anatomical disposition. A gastric suction tube and intravenous drip are employed postoperatively until flatus is passed and bowel sounds are satisfactory; continuous suction is always applied if the abdomen becomes distended. With this routine, in about 50 patients no alarming ileus has been observed, although in 2 small-bowel obstruction developed owing to adhesions and required further operation.

Treatment of the Causal Disease—Atherosclerosis

The surgeon dealing with such cases as those described here is merely putting right the most obvious expression of the generalised state of atherosclerosis. Progressive atherosclerosis not only will jeopardise the " graft " but also may involve the opposite limb or disable the patient by coronary thrombosis.

Most of our patients operated on for occlusive disease were given long-term anticoagulant therapy. It is obviously difficult to obtain convincing evidence on the value of this therapy; as the results show, it does not provide complete protection from graft closure or further expressions of atherosclerosis, but it may provide some measure of protection. The evidence requires further study and we hope to analyse our experience later.

Obese patients were urged to follow a weight-reducing diet; in patients with occlusion of the abdominal arteries, we often insisted on this before undertaking surgery, partly to facilitate the operation (a very real advantage) and partly because we considered obesity highly disadvantageous to the atherosclerotic patient. The patients were encouraged to take regular exercise before and after operation because physical inactivity was thought to be another adverse factor; smoking, although not forbidden, was discouraged. A diet of unsaturated fats was not imposed on the patients, but they were advised to avoid eating large quantities of fat. As with anticoagulants, it is impossible to assess the value of these measures. Without doubt weight reduction was of value to the patients, and many expressed relief at the improvement in their general well-being after losing one or two stone in weight. The advantages of driving a bargain with the patient to do the operation after he had lost weight were quite obvious.

Summary

Five years' experience of operations for arterial replacement and reconstruction on account of aneurysm or occlusive disease of arteries is reviewed.

Evidence is given that homografts lack durability and should usually be avoided. Arterial prostheses of crimped 'Dacron' ('Terylene') proved very satisfactory and apparently more durable.

Disastrous results may follow infection of any form of arterial prosthesis, and thus reconstruction of the patient's own arteries, whenever this is feasible, is to be preferred.

Replacement of abdominal aortic aneurysms by a homograft and plastic prosthesis proved satisfactory. Of patients with a leaking abdominal aortic aneurysm who reach the operating-theatre alive, about half survive, and the survivors may remain well for some years.

Abdominal-aortic and iliac-artery occlusion or narrowing responds well to thromboendarterectomy. Good results can be obtained by restoring a pulsatile flow in the profunda femoris even if the superficial femoral arteries are closed. In younger patients aortic occlusion may be misdiagnosed as Buerger's disease. In the presence of aortic or iliac-artery occlusion, impending gangrene of the lower extremities can be consistently relieved by reopening these vessels.

In occlusion of the superficial femoral or popliteal arteries, bypass " grafting " gives good results over long periods in patients with simple claudication. When rest pain or actual gangrene is present the benefit tends to be short-lived and it is often not possible to avert amputation.

Thromboendarterectomy is satisfactory in the common femoral artery or in the major abdominal arteries, but in the superficial femoral and popliteal arteries thromboendarterectomy using a ring stripper is usually less successful.

REFERENCES

Barratt-Boyes, B. G. (1957) *Lancet*, ii, 716.
Cannon, J. A., Barker, W. F., Kawakami, I. G. (1958) *Surgery*, **43**, 76.
Crawford, E. S., De Bakey, M. E., Cooley, D. A. (1958) *Arch. Surg., Chicago*, **76**, 261.
Duguid, J. B. (1946) *J. Path. Bact.* **58**, 207.
— (1948) *ibid.* **60**, 57.
— (1955) *Practitioner*, **175**, 241.
— (1960) *Postgrad. med. J.* **36**, 226.
Eastcott, H. H. G., Holt, L. B., Peacock, J. H., Rob, C. G. (1954) *Lancet*, i, 1311.
Estes, J. E. (1950) *Circulation*, **2**, 258.
Fisher, B., Adams, C., Wilde, R., Fisher, E. R. (1956) *Ann. Surg.* **143**, 73.
Flewett, T. H., Zinneman, K. S., Oldfield, M. W. C., Shucksmith, H. S., Dexter, F. (1955) *Lancet*, i, 888.
Hardy, E. G., Tibbs, D. J. (1960) *Brit. med. J.* i, 1001.
Julian, O. C., Deterling, R. A. Jr., Dye, W. S., Bhonslay, S., Grove, W. J., Belio, M. L., Javid, H. (1959) *Arch. Surg., Chicago*, **78**, 260.
Szilagyi, D. E., McDonald, R. T., Smith, R. F., Whitcomb, J. G. (1957) *ibid.* **75**, 506.
Tibbs, D. J. (1960) *Postgrad. med. J.* **36**, 283.
— Leslie, W. G. (1958) *Lancet*, i, 1158.

Addendum

The trends described above have been maintained over the four months since this article was written.

The patients being followed up have remained well with 2 exceptions. A femoropopliteal dacron bypass graft, inserted on account of simple claudication, has closed off after functioning for one year. Around another femoropopliteal dacron bypass graft, inserted two years previously

on account of gangrene of the toes in a diabetic patient, a massive abscess developed, and, although still functioning, the graft had to be removed; *Staphylococcus aureus* was grown from the abscess and from a septic lesion on the corresponding foot.

20 further operations of arterial reconstruction or replacement have been undertaken successfully, but 1 patient has died postoperatively from infection with a *Staph. aureus* prevalent in the ward. 2 ruptured abdominal aortic aneurysms have been encountered: 1 was successfully operated upon, but in the other case the patient died before he reached the operating-theatre.

BRONCHODILATORS AND CORTICOSTEROIDS IN ASTHMA

Forced Expiratory Volume as an Aid to Diagnosis and Treatment

K. M. HUME
M.D. Lond.
ASSISTANT MEDICAL OFFICER
E. RHYS JONES
M.B., B.Sc. Wales, M.R.C.P.
FIRST ASSISTANT MEDICAL OFFICER
KING EDWARD VII SANATORIUM, MIDHURST, SUSSEX

SPIROMETRIC investigation is now used in many chest units to determine whether wheezing and dyspnœa are due to the remediable condition, reversible bronchospasm, or to permanent bronchial narrowing, which will not respond to bronchodilator therapy, associated with diseases such as emphysema or fibrosis of the lung. The usual test is the forced vital capacity, which is a single forced expiration recorded with a spirometer (Bernstein et al. 1952); and the initial part of the expiration, commonly the volume expired in the first second (the forced expiratory volume in one second, $F.E.V._{1\cdot0}$), is a more reliable index than the value for the total expiration. When bronchial narrowing is present the value obtained decreases; and if, after administering a bronchodilator, this increases, it can be deduced that the bronchodilator is effective.

By repeating these tests daily we obtained different response patterns in asthma and in the other diseases which may cause wheezing, and even in the various forms of asthma itself. Here we report the method of investigating wheezing and also how, by daily tests, the best way to use bronchodilator and corticosteroid therapy can be determined. The results of two trials (Hume and Gandevia 1957, Hume and Rhys Jones 1960) will serve to illustrate how this method can be applied in the clinical management of patients. In both trials the $F.E.V._{1\cdot0}$ was measured daily in patients from the time they were admitted to hospital in status asthmaticus until they had completely recovered.

Recording of $F.E.V._{1\cdot0}$

Before and after Inhaled 1% Isoprenaline

Complete readings for one patient are shown in fig. 1; the daily initial $F.E.V._{1\cdot0}$ is plotted against the $F.E.V._{1\cdot0}$ after administering 1% isoprenaline as aerosol.

When intrinsic asthma was very severe, as indicated by low initial $F.E.V._{1\cdot0}$ values, little improvement followed inhalation of isoprenaline. As the asthma responded to treatment over the ensuing days and the pre-inhalation $F.E.V._{1\cdot0}$ rose, so the improvement resulting from the inhalation of isoprenaline increased until the maximum response for that patient was obtained when all bronchial constriction was reversed. Thereafter the pre-inhalation

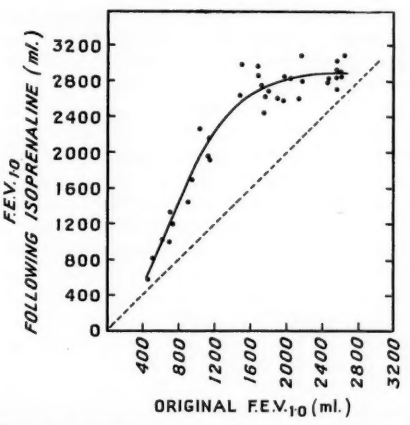


Fig. 1—Forced expiratory volume in first second before and after aerosol isoprenaline.

$F.E.V._{1\cdot0}$ approached the now constant post-inhalation value. The curve for fig. 2 (patient A) shows the same results plotted in a more useful way with the figure for the pre-inhalation or initial $F.E.V._{1\cdot0}$ subtracted from the post-inhalation value so that the ordinate measures the improvement resulting from the inhalation of isoprenaline.

Before and after Aerosol Isoprenaline, Intravenous Aminophylline, and Aerosol Atropine singly and in Combination

In the second trial (Hume and Rhys Jones 1960) response curves similar to those for isoprenaline were obtained for other bronchodilators, irrespective of their route of administration. The incomplete response to bronchodilator therapy in status asthmaticus was considered to be due to local change in the fibres of the contracted bronchial muscle and not to tolerance to any one type of bronchodilator. Corticosteroid therapy is beneficial principally because it resolves this factor which is operating in addition to simple muscle spasm.

The maximum response to a bronchodilator, though limited when asthma was severe, was reached with a low dosage, but if a second bronchodilator with a different pharmacological action was then administered, the $F.E.V._{1\cdot0}$ improved further. The order in which the drugs were

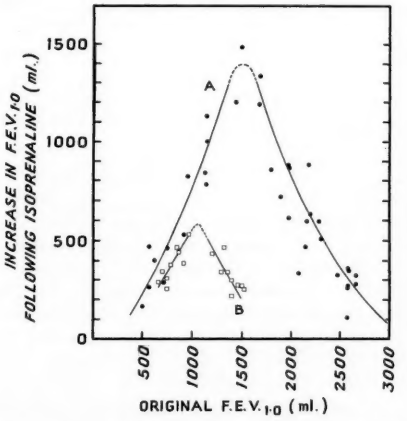


Fig. 2—Data of fig. 1 plotted with improvement in the forced expiratory volume in first second as ordinate.

Patient A is the one with intrinsic asthma in Fig. 1. Patient B shows the nature of the response when intrinsic asthma coexists with emphysema.

given affected the response; thus intravenous aminophylline after 1% isoprenaline as aerosol was generally more effective than when the drugs were administered in the reverse order.

Diagnosis

Recurrent attacks of wheezing in adults may be due to intrinsic or extrinsic asthma. Clinical differentiation is often possible; intrinsic asthma characteristically appears for the first time in adult life in the absence of demonstrable allergens in the environment outside the body, and the attacks become progressively longer and more frequent until, within a few years, the patient is rarely free from chronic wheezing upon which acute attacks of status asthmaticus, responding poorly to bronchodilators, are superimposed. Extrinsic asthma, on the other hand, frequently appears in childhood and is triggered off by external allergens; and the attacks, although acute, are often short, commonly responding dramatically to bronchodilator therapy. But the nature of the asthma may vary and the extrinsic form may change into the intrinsic when the patient reaches adult life. Clinical diagnosis is further complicated because the forms are not entirely age-specific and, particularly in intrinsic asthma, also because of coexisting emphysema. The presence of

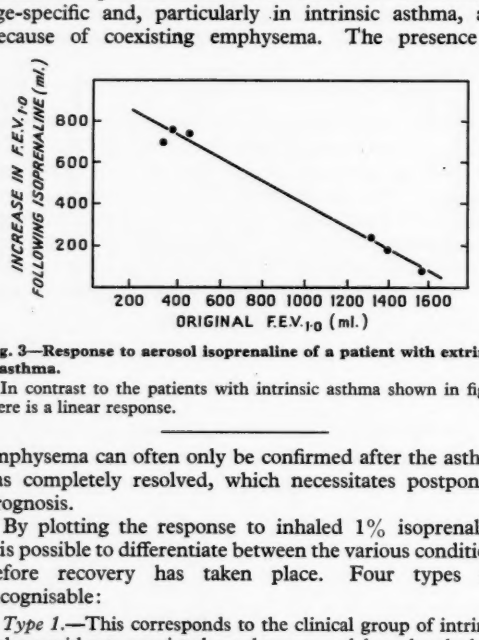


Fig. 3—Response to aerosol isoprenaline of a patient with extrinsic asthma.
In contrast to the patients with intrinsic asthma shown in fig. 2 there is a linear response.

emphysema can often only be confirmed after the asthma has completely resolved, which necessitates postponing prognosis.

By plotting the response to inhaled 1% isoprenaline it is possible to differentiate between the various conditions before recovery has taken place. Four types are recognisable:

Type 1.—This corresponds to the clinical group of intrinsic asthma without associated emphysema and has already been illustrated (patient A, fig. 2).

Type 2.—This is found in patients with uncomplicated extrinsic asthma in whom the bronchodilator effect is maximal even when the F.E.V.$_{1\cdot0}$ is low. The results in this type of asthma are shown in fig. 3. It was not possible to test the patient over a wide initial-F.E.V.$_{1\cdot0}$ range because complete recovery followed the administration of isoprenaline. The three left-hand tests where the original F.E.V.$_{1\cdot0}$ was low were performed during three separate attacks of asthma. In each case the test next day showed that the effect of the isoprenaline had been maintained and hardly any bronchospasm was present.

The patient, a woman, aged 23, had had short-lived acute attacks of asthma since childhood. Although external allergens could not be identified, her attacks were readily triggered off by colds and emotional upsets; and the nature of the attacks, which responded rapidly and completely to bronchodilators, conformed to the pattern of extrinsic asthma.

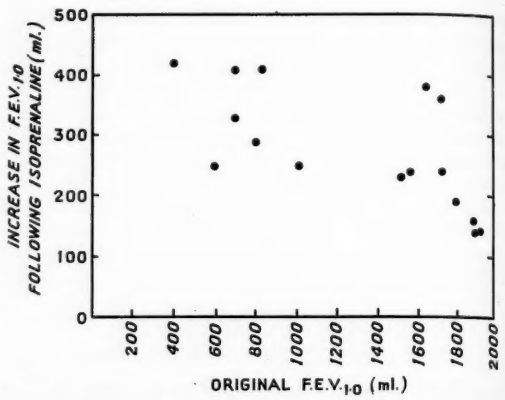


Fig. 4—An intermediate response in a patient in the transitional phase between extrinsic and intrinsic asthma.

Type 3.—Only two patients fell into this category; but the clinical history suggested that it may be a separate entity of particular interest, representing the change-over from extrinsic to intrinsic asthma. The results for one of the patients are shown in fig. 4. There was an incomplete response, intermediate between those in types 1 and 2, to the bronchodilator when the original F.E.V.$_{1\cdot0}$ was low. When the original F.E.V.$_{1\cdot0}$ exceeded about 1600 ml. the response was the same as in patient A (fig. 2), as might have been expected when the full bronchodilator response was reached.

Both patients were young men, aged 20 and 28, who had had typical attacks of extrinsic asthma since childhood, which had recently changed in character, the attacks becoming more long drawn-out and resistant to bronchodilator therapy.

Type 4.—Coexistent emphysema is disclosed by one of two types of response, according to whether asthma with emphysema, or emphysema with reversible bronchial construction, predominates. Patient B (fig. 2) exemplifies the first of these two groups of cases.

This patient, a woman aged 45, had had attacks of asthma for 40 years, which had over the past 10 years, during which she had attended this hospital, been intrinsic in nature. She had clinical and radiological evidence of advanced emphysema.

The results have been included in fig. 2 for comparison with those in patient A with uncomplicated intrinsic asthma. The peak of the response curve is considerably lower in patient B, and extrapolation of the right-hand limb to the abscissa gives a maximum F.E.V.$_{1\cdot0}$ for the patient of 1700 ml., whereas the predicted normal value is 2400 ml.

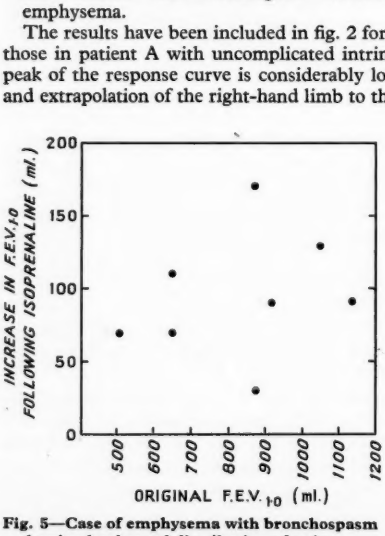


Fig. 5—Case of emphysema with bronchospasm showing haphazard distribution of points.
Note reduction in the ordinate scale.

When emphysema is the primary disease, and reversible bronchial constriction is secondary, the results do not follow any particular pattern and characteristically are distributed haphazardly

is is shown in fig. 5, so that no curve can be fitted to them. Why the response to bronchodilators is so variable and unpredictable is not clear, but we feel it may be due to other mechanical factors resulting from the emphysema.

In these cases patients with asthma can be distinguished from those with asthma and emphysema by expressing the F.E.V.$_{1\cdot0}$ as a percentage of the vital capacity (Thomson and Hugh-Jones 1958).

Treatment

Intrinsic asthma with status asthmaticus is usually treated at first with bronchodilator drugs and antibiotics, corticosteroids being withheld while the effect of this treatment is observed (Medical Research Council 1956). When the attack has been precipitated by a factor, such as a fresh infection, which can be overcome by appropriate antibiotics, this treatment may tide the patient over the relapse. Frequently, however, clinical improvement is slow and the result disappointing and then corticosteroid therapy must be considered.

Corticosteroids are valuable in the treatment of intrinsic asthma, both in acute status asthmaticus and also for maintenance therapy in cases which will otherwise relapse when treatment is withdrawn. Indications for corticosteroid therapy should be clearly defined because even the latest corticosteroids have serious side-effects limiting their use. Clinical assessment of a case presents many difficulties. The natural course of the disease is very variable, both in different cases and in the different phases in any one patient. Factors such as infection, reversible bronchial constriction, and irreversible changes in the bronchi and lung parenchyma all contribute to the clinical manifestations. Each has to be considered in relation to the duration, frequency, and severity of the asthmatic attacks, and no single factor provides a satisfactory clinical yardstick to determine the need for steroids.

The most obvious requirement is a diagnostic method to distinguish cases which will respond to bronchodilators from those which require corticosteroids. Coexisting emphysema must also be detected; this adversely affects the prognosis and makes it even more important to control any bronchial obstruction in order to avoid progressive emphysematous change. Accurate diagnosis can be achieved with the daily F.E.V.$_{1\cdot0}$ tests; over the past four years we have used this method, together with clinical criteria, to decide on the treatment of severe asthma.

When a patient is admitted, a clinical assessment is made. If the attack is very severe and the asthma must be relieved at once, corticosteroid therapy with corticotrophin drip is started immediately. If the patient's life is clearly not in immediate danger, energetic bronchodilator therapy with 1% isoprenaline as aerosol and intravenous aminophylline is begun. The F.E.V.$_{1\cdot0}$ before and after inhaled isoprenaline is first measured as soon as practicable, with regard to the fact that when wheezing is very severe the patient must rest and the expiratory effort necessary to perform the F.E.V.$_{1\cdot0}$ may be exhausting and may even temporarily increase the wheezing (Hume 1959). The optimum bronchodilator effect results from administering relatively small doses of the drugs—in the case of isoprenaline the inhalation of a 1% solution for thirty seconds, and in the case of aminophylline an intravenous injection of 0·25 g. (Hume and Rhys Jones 1960). In these low doses these drugs can exert their maximum therapeutic effect without causing side-effects. Furthermore, the trial demonstrated that, when the initial F.E.V.$_{1\cdot0}$ is low, although the maximum effect of any one bronchodilator may be clinically undetectable, tests will show that improvement has occurred. A greater improvement was observed when two or more bronchodilator drugs of different pharmacological groups were employed. The order in which the drugs were given was important: sympathomimetic drugs such as isoprenaline should be given before the parasympathetic-blocking atropine, or aminophylline.

The F.E.V.$_{1\cdot0}$ tests are repeated daily during bronchodilator therapy; some patients make steady progress and ultimately recover. But if after a week there is no improvement in the daily initial F.E.V.$_{1\cdot0}$ value, and the patient remains in status asthmaticus, corticosteroid therapy is commenced, with 30 mg. of prednisone daily: rapid improvement, as shown by the daily F.E.V.$_{1\cdot0}$ figure, is almost invariable. The bronchodilator drugs become more effective, and the patient's response resembles that of patients A and B (fig. 2). When the patient's response has passed the peak of the curve and lies on the descending limb, and bronchodilator effect is maximal, the corticosteroid is gradually reduced but bronchodilator therapy is maintained. Daily F.E.V.$_{1\cdot0}$ tests will show any decrease in the value as the corticosteroid is withdrawn. Complete withdrawal is possible in some patients; their response remains to the right of the peak of the curve—i.e., they remain fully responsive to bronchodilators. But in the majority of patients the daily F.E.V.$_{1\cdot0}$ decreases in value and the response once again approaches the peak of the curve and reverses down the left-hand limb. These patients require bronchodilator therapy combined with corticosteroids for maintenance.

Observations on patients after relapse, while either they were receiving a reduced dose of corticosteroid or after the drug had been completely withdrawn, showed that adjusting the treatment caused the test results to follow the response curve originally plotted.

We have tested patients within a few hours of relapse, when the response lies to the left of the peak of the curve. The effect in these cases has been greater than expected; the isoprenaline was still apparently exerting a maximum effect, and the patient with intrinsic asthma was responding like one with extrinsic asthma. But this maximal response lasted only 48 hours, and if corticosteroid dosage was not adjusted the improvement after inhaled isoprenaline reverted to the level of the left-hand limb of the original curve.

This observation suggested that there was a " latent period " of about 48 hours before changes in the bronchial muscle resulted in a recurrence of the " drug-fast state ". It also underlined the importance of observing patients closely, and performing daily tests, while corticosteroid dosage was being reduced.

Patients were not deeply aware of respiratory disability when the value of the F.E.V.$_{1\cdot0}$ was at the level associated with maximum isoprenaline response (the peak of the curve) (Hume and Gandevia 1957). We agree that a satisfactory way to determine the minimum corticosteroid dosage for maintenance is to maintain the value of the F.E.V.$_{1\cdot0}$ on the right-hand limb of the curve near the peak rather than attempt to achieve an asthma-free state. At this F.E.V.$_{1\cdot0}$ level the patients remained fully responsive to bronchodilators on the minimum maintenance dosage of corticosteroids.

From the response curve for a patient with intrinsic asthma requiring maintenance corticosteroids and bronchodilators, we can rapidly determine which group of drugs to

increase in dosage when relapse threatens. If the F.E.V.$_{1\cdot0}$ decreased and the value lay on the left-hand limb (and full bronchodilator response was not obtained), we found that the patient was liable to develop status asthmaticus unless the corticosteroid dosage was increased. But if the figure for F.E.V.$_{1\cdot0}$ lay at the peak or to the right of it, then increasing the dosage of bronchodilators was usually enough to prevent severe asthma.

Of the two patients whose response resembled the pattern shown in fig. 3, one required corticosteroids both in attacks of status asthmaticus and for maintenance, while the other responded to antibiotics and bronchodilators alone. The patient requiring corticosteroids was picked out by testing as above.

The treatment of patients with emphysema and reversible bronchospasm (fig. 4) is not the same as of those we have discussed in whom, although some emphysema may coexist, asthma is the major disability.

As a rule, the primarily emphysematous patients respond to bronchodilator therapy, but even when bronchospasm is relieved they may still have incapacitating dyspnœa due to irreversible changes in the lung parenchyma and bronchi. But some do not respond satisfactorily to bronchodilators, apparently as a result of producing excess of mucoid or mucopurulent sputum. Appreciable improvement in these patients can be obtained with corticosteroids, since these reduce the amount of sputum. Withdrawal of corticosteroids will have to be carried out over longer periods in these patients, in whom, possibly because of their high average age, the adrenals appear unable to function again; this must be borne in mind before starting corticosteroid therapy.

Summary

Daily measurement of the forced expiratory volume is of value in the diagnosis and treatment of patients with a chronic wheeze due to asthma, emphysema, or both.

The forced expiratory volume in the first second (F.E.V.$_{1\cdot0}$) is more reliable for this purpose than the complete forced vital capacity.

Five different patterns of response of diagnostic significance are obtained when 1% isoprenaline is inhaled as an aerosol.

F.E.V.$_{1\cdot0}$ measurements can be used in treatment to determine whether corticosteroids are needed to supplement the bronchodilator drugs.

We wish to thank Sir Geoffrey Todd for advice in the preparation of the paper; Boots Ltd. for supplies of intravenous aminophylline; and Messrs. Allen & Hanburys Ltd. for statistical advice.

REFERENCES

Bernstein, L., D'Silva, J. L., Mendel, D. (1952) *Thorax*, **7**, 255.
Hume, K. M. (1959) *in* Bronchial Asthma (Chest and Heart Association, London); p. 35.
— Gandevia, B. (1957) *Thorax*, **12**, 276.
— Rhys Jones, E. (1960) *Quart. J. Med.* (in the press).
Medical Research Council (1956) *Lancet*, ii, 803.
Thomson, W. B., Hugh-Jones, P. (1958) *Brit. med. J.* i, 1093.

"... There is a very ancient belief that health is a simple state, to be attained by observing a few simple positive and negative rules ... But it follows from the complexity of the body that health cannot be a simple state. ... Because there are literally thousands of ways of being ill, to be well one has to be well in thousands of ways at once. ... Though a healthy person will have neither diphtheria nor diabetes, he will not escape them because he is healthy, but he will be healthy because he has not got them."—Sir RUSSELL BRAIN, Osler memorial oration to Canadian Medical Association, 1960. *Pharos*, October, 1960, p. 185.

RUPTURE OF THE INTERVENTRICULAR SEPTUM ASSOCIATED WITH ACUTE MYOCARDIAL INFARCTION

K. F. R. SCHILLER
M.A., B.M. Oxon., M.R.C.P.
MEDICAL REGISTRAR, THE LONDON HOSPITAL, E.1

THE physical signs in a patient who died from rupture of the interventricular septum (I.V.S.) following myocardial infarction were first described by Latham (1845). Although several descriptions of this condition appeared over the next few years—e.g., Galt (1909)—Brunn (1923) made the first correct diagnosis during life. The first successful operation for ruptured I.V.S. following myocardial infarction was performed by Cooley et al. (1957). Perforation of the I.V.S. in association with myocardial infarction is uncommon: Sanders et al. (1956) could collect only 124 cases, adding 8 of their own. Other small series have since appeared—e.g., Malone and Parkes (1955) and Swithinbank (1959). Here I describe 7 further cases, in 6 of which the diagnosis was made during life.

Case-records

Case 1.—A man, aged 73, was admitted on Feb. 25, 1950. Five days before admission he had collapsed with severe chest pain. Symptoms eased, but returned on Feb. 25.

Examination and course.—The patient was profoundly shocked, with an impalpable pulse and unrecordable blood-pressure. The apex beat was in the anterior axillary line. There was a loud precordial systolic murmur. Despite emergency treatment, the patient died soon after admission. An electrocardiogram (E.C.G.) was not taken.

Necropsy

The heart weighed 520 g. The left ventricle was hypertrophied. A soft yellowish area of recent infarction was found in the posterior and upper thirds of the I.V.S. and in the whole of the posterior wall of the left ventricle. There was a vertical rent 4 cm. long through the upper part of the I.V.S. at its junction with the posterior wall. A recent thrombus occluded the right coronary artery for 1·7 cm. before the start of the posterior descending branch. Older recanalised thrombi were found in the right and circumflex coronary arteries.

Postmortem diagnosis: intramuscular rupture of the heart from recent infarction, with fresh thrombus in an atheromatous coronary artery; also old coronary thromboses.

Case 2.—A man of 60 was admitted on Jan. 4, 1955. Two days before admission, he had had severe retrosternal chest pain radiating to the back and lasting thirty minutes. On the day of admission the pain returned after mild exertion.

Examination and course.—The patient was a plethoric fit-looking man in no apparent distress; pulse-rate 74, blood-pressure 200/115 mm. Hg, apex beat diffuse, heart sounds normal, no evidence of shock or congestive cardiac failure. E.C.G. (fig. 1a) showed a QS pattern in CR_1, CR_2 and CR_4, with RST elevation in I and all chest leads, and T inversion in II and III. He was treated symptomatically for acute myocardial infarction. Anticoagulants were not given at this stage. Two days later there was a rise in pulse-rate and in temperature. His condition was then much worse, with cyanosis, blood-pressure 120/70, and raised jugular venous pressure. A loud systolic murmur over the precordium obscured the heart sounds. Crepitations were present over both lung bases. Rupture of the I.V.S. was diagnosed and anticoagulant therapy started. The blood-pressure continued to fall and congestive cardiac failure supervened. E.C.G. showed no new changes. A day later a systolic thrill became palpable over the precordium. On Feb. 16 a phonocardiogram (incomplete because of the patient's poor condition) was recorded; this showed a large systolic murmur with a small gap before the second sound. The congestive cardiac failure, however, proved intractable; and the patient died on March 15, 1955.

Necropsy

The heart weighed 420 g., and both ventricles were slightly dilated. The left ventricular wall over the anterior apical portion was thinned to 0·3 cm., with an aneurysmal dilatation. A thinned area of old cardiac infarction extended over the anterior 3 cm. of the I.V.S., enclosing a small round-bordered septal defect at the junction of the upper two-thirds and lower third of the septum (fig. 2). There was fresh infarction of the left ventricle. The left descending coronary artery was occluded by soft brown thrombus for 1 cm. about 3 cm. from the artery's origin.

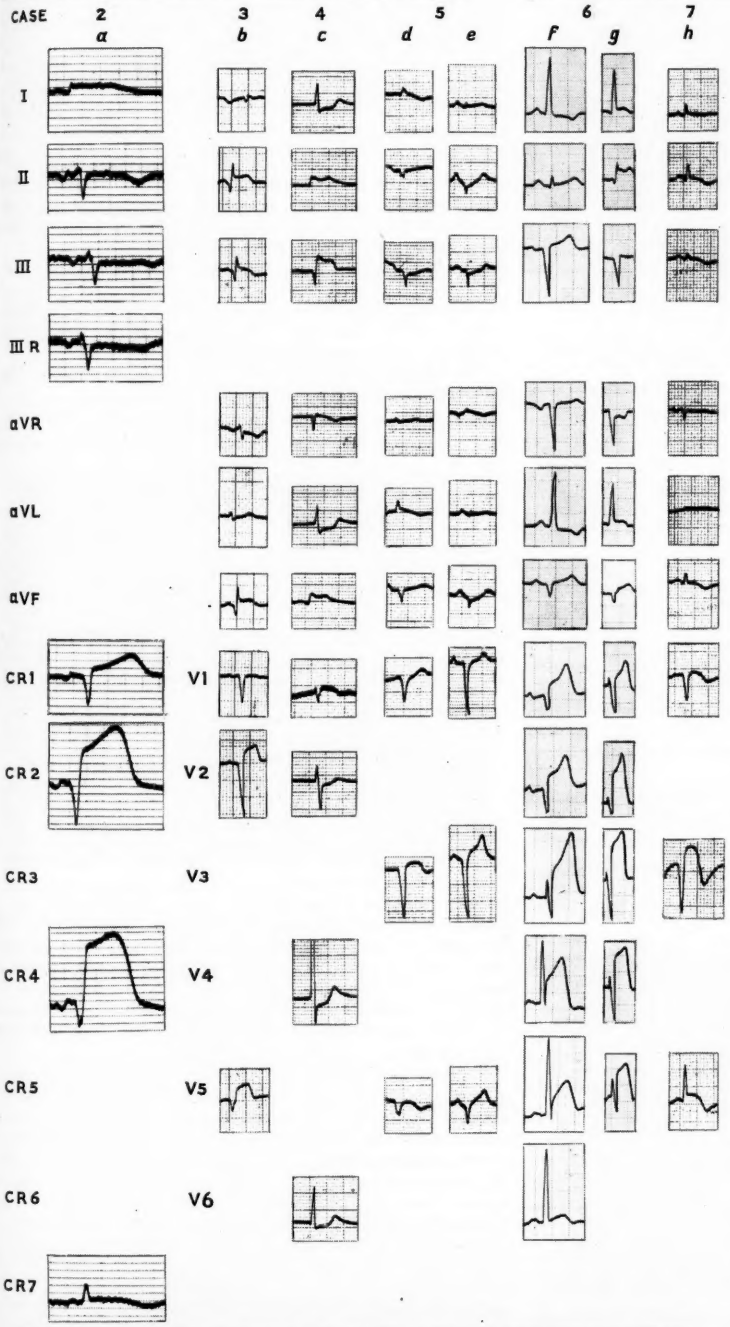


Fig. 1—Electrocardiograms from 6 patients with rupture of interventricular septum.

Postmortem diagnosis: defect of I.V.S. from rupture of recently infarcted myocardium; old cardiac infarction.

Case 3.—A signalman of 49, with no serious previous illnesses, was admitted on March 22, 1956, complaining of sudden severe epigastric pain associated with nausea and vomiting.

Examination and course.—The patient was an obese man, in obvious pain. His blood-pressure was 140/100 mm. Hg, with normal heart sounds and no precordial murmurs. On March 26 he had a loud harsh pansystolic murmur loudest over the apex; no thrill was felt. The jugular venous pressure was elevated. E.C.G. (fig. 1b) showed deep Q waves together with definite RST elevation in leads I, II, III, aVF, V_3, and V_6, and flattening of T waves in V_1. A diagnosis of acute cardiac infarction was therefore confirmed, though the significance of the systolic murmur was not appreciated. Congestive cardiac failure and attacks of acute left ventricular failure were treated, and the patient was given anticoagulant therapy. Later, a precordial thrill was felt, and rupture of the I.V.S. was tentatively suggested. The patient never rallied, rhythm changes supervened, and he died on May 27, 1956.

Necropsy

The heart, which weighed 514 g., showed right ventricular and left ventricular dilatation. The apical two-thirds of the septum was replaced by a thin fibrous scar in the middle of which there was a rent 1 cm. long, about 2 cm. from the apex. The apical third of the rest of the left ventricular wall was extremely thin but not fibrosed. A large plaque of atheroma almost obstructed the left main coronary artery 2 cm. from its bifurcation.

Postmortem diagnosis: perforated septal cardiac infarct, with underlying myocardial fibrosis.

Case 4.—A woman of 62 was admitted on Dec. 19, 1957. On Dec. 15 she had had an attack of severe retrosternal pain radiating to the chin, accompanied by nausea and vomiting. Acute myocardial infarction was diagnosed, and she was ordered bed rest at home; anticoagulants were not prescribed. No systolic murmur was heard. On the evening before admission the pain returned, and this persisted to the next morning when her doctor referred her to hospital.

Examination and course.—On admission the patient was very ill and was mentally confused. She was pale and sweating and had a feeble irregular pulse, elevation of jugular venous pressure, and an unrecordable blood-pressure. The apex beat was not felt; the heart sounds were faint but there was a loud harsh pansystolic murmur, best heard over the apex; diastole was clear. Crepitations were present at the bases of the lungs. E.C.G. (fig. 1c) showed atrial fibrillation, with deep Q in lead III and elevation of the RST segment

Fig. 2—Case 2: heart from left ventricular aspect, showing rupture of interventricular septum of 2 months' standing.

in leads II, III, and aVF. T in V_2 was a little flattened. Acute myocardial infarction with perforation of the I.V.S. was diagnosed. The patient was treated with intravenous heparin and noradrenaline, without response. An E.C.G. the day after admission showed no significant changes. The patient died a few hours later.

Necropsy

The heart weighed 410 g. and showed early left ventricular hypertrophy. On the left side of the I.V.S. there was a large ragged area 2 cm. in diameter about 3 cm. from the apex (fig. 3). Despite some organised clot, there was free communication between the two ventricles through this interventricular tear. Fresh thrombus was found in the right coronary artery, 0·5 cm. from its origin, completely occluding the lumen (fig. 4). In addition, there were bilateral pleural effusions and considerable congestion of lungs and liver.

Postmortem diagnosis: ruptured I.V.S. following acute myocardial infarction due to thrombosis of right coronary artery.

Case 5.—A woman of 77 was admitted on July 9, 1958. For some months she had had exertional chest pain and dyspnœa. On the day of admission she suddenly felt a crushing central chest pain radiating to the left arm, associated with nausea and vomiting.

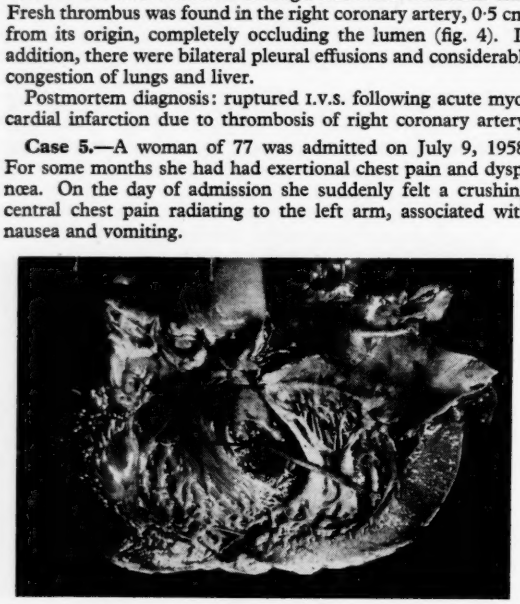


Fig. 3—Case 4: heart from left ventricular aspect, showing rupture of interventricular septum of 2 days' standing.

Examination and course.—The patient was fully conscious, shocked, and in severe pain. Pulse-rate 100 per min., blood-pressure 150/100 mm. Hg; there was central cyanosis, and jugular venous pressure was increased. Crepitations were heard in both lung bases. The clinical diagnosis of acute myocardial infarction was confirmed by E.C.G. which showed large Q waves in leads II, III, aVF, and the V leads, together with RST elevation and T inversion in leads I, aVL, V_3 and V_5 (fig. 1d). The patient was treated with bed rest; anticoagulants were not prescribed. On July 16 there was a loud pansystolic apical precordial murmur, but no evidence of congestive cardiac failure. Perforation of the I.V.S. was diagnosed. Next day there was deterioration with a fall in blood-pressure and rise of jugular venous pressure. Despite symptomatic treatment, the patient's condition did not improve. E.C.G. taken on Aug. 7 (fig. 1e) showed no evidence of further infarction. She died next day.

Necropsy

The heart weighed 330 g.; the right ventricle was slightly hypertrophied. In the upper portion of the left ventricle the muscle was hypertrophied; but the apex involving the anterior, lateral, and posterior walls was thin (0·2 cm.), being made up of fibrotic tissue and thickened endocardium. The apex of the left ventricle was part of a ventricular aneurysm. The septal wall was also thin, being perforated at its lowest portion by a fibrin-covered rent 0·8 cm. long. The coronary arteries were atheromatous with evidence of recanalisation.

Postmortem diagnosis: rupture of I.V.S. following recent myocardial infarction and old myocardial fibrosis.

Case 6.—A retired engineer of 67 was admitted on April 20, 1959. He had had hypertension since 1941. He had been

Fig. 4—Case 4: fresh thrombus in right coronary artery.

investigated for anæmia in 1954, when his blood-pressure was 170/110 mm. Hg. Manifestations of cerebral arteriosclerosis were observed over the following years. He had never had angina pectoris or undue effort dyspnœa. On April 18, 1959, he had an attack of severe pain between the shoulder-blades, associated with dyspnœa. This became worse, and admission was requested.

Examination and course.—The patient was an obese apyrexial man in no obvious distress. Pulse-rate 100 per min. regular, blood-pressure 180/110, jugular venous pressure raised to 4 cm., apex beat 5th left intercostal space in the anterior axillary line, heart-sounds normal without murmurs or thrills. E.C.G. (fig. 1f) showed RST elevation in II, III, aVF, V_1–V_6, with T inversion in I and aVL, confirming the clinical diagnosis of acute myocardial infarction. Anticoagulant therapy was instituted. During the next four days he became confused. On April 26 there was sudden deterioration with arrhythmia and fall of blood-pressure to 110/70. E.C.G. (fig. 1g) showed atrial fibrillation, RST elevation in I as well as in all other leads, with increased elevation in leads II, III, aVF, V_1–V_6. Blood-urea

was 300 mg. per 100 ml. On May 1 there was a loud pansystolic murmur obscuring the normal heart-sounds, being best heard at the left sternal edge in the 4th left interspace. There were some slight signs of congestive cardiac failure. Rupture of the I.V.S. was diagnosed. The patient was digitalised, but slowly deteriorated. He lapsed into coma, and died on May 7.

Necropsy

The heart was enlarged, weighing 750 g. There was extensive infarction of heart muscle involving the apex, lower half of the anterior left ventricular wall and septum, and lower two-thirds of lateral and posterior left ventricular walls. An irregular perforation of the I.V.S. was found in its lowest part, measuring 1·5 cm. across. The coronary arteries were narrowed throughout. There was incomplete obstruction of the left main coronary artery, 2·5 cm. distal to the origin on the descending branch which was completely occluded.

Postmortem diagnosis: cardiac infarction with perforation of the I.V.S.; generalised atherosclerosis.

Case 7.—A carpenter of 61 had been without exertional chest pain, or dyspnœa until May 2, 1959, when he felt severe epigastric pain without nausea, sweating, or vomiting. He was seen in a casualty department where his blood-pressure was 200/120 mm. Hg, and there were no other abnormal physical signs. He was treated with sedatives and antacid powders. Vague left precordial discomfort developed over the next two days, and he was admitted on May 4, 1959.

Examination and course.—The patient looked fit and was in no obvious pain. There was no cyanosis and the limbs were warm; his blood-pressure was only 90/60; pulse-rate 120, regular; no jugular venous pressure; lung bases dry. A systolic thrill was felt over the lower sternum, and the heart-sounds were obscured by a loud pansystolic murmur maximal over the apex, radiating to the axilla. Acute myocardial infarction with subsequent rupture of the I.V.S. was diagnosed. E.C.G. (fig. 1h) showed the greatest RST elevation in V_3, but it was also present in leads II, aVF, and all the V leads, together with T inversion in these leads, and a distinct QS pattern in V_1 and V_3. Anticoagulant therapy was started, and later, in view of congestive cardiac failure, digitalis was added. Despite this, the congestive cardiac failure proved intractable and attacks of acute left ventricular failure supervened. Hypotension developed; and, after a hæmatemesis, the patient died on May 31.

Necropsy

The pericardial sac was found to contain a little blood, with petechial hæmorrhages over the posterior surface of the heart. The heart (418 g.) showed early right ventricular hypertrophy. There was a triangular tear in the lower part of the I.V.S. about 1·5 cm. across, the upper edge being a little rounded while the lower edges were rough. There was obvious recent infarction of the surrounding septum and anterior wall of the left ventricle which showed some generalised hypertrophy. All coronary arteries were atheromatous, with obliterations, in one place, of the lumen of the anterior descending branch. In addition, there was evidence of congestive cardiac failure, and of gastro-intestinal hæmorrhage without obvious cause.

Postmortem diagnosis: rupture of the I.V.S. following recent acute infarction of the left ventricle and septum due to coronary occlusion; also acute gastrointestinal hæmorrhage.

The data on these 7 cases are summarised in the accompanying table.

ANALYSIS OF 7 CASES

Sex-distribution	5 men; 2 women
Av. age (yr.)	64
Hypertension before recent infarction	Only 1 definite
After recent infarction:	
Persistent hypertension	3
Anticoagulants	1
Pressor agents	0
Av. interval (days) between infarction and perforation	About 5
After perforation:	
Mode of onset of symptoms	Insidious in 5; sudden in 2
Systolic murmur	7
Systolic thrill	3
Diastolic murmur	Nil
Congestive cardiac failure	6. 2 also had left ventricular failure
Left ventricular failure	2, both with congestive cardiac failure
Other complications	1 jaundice and hæmorrhage 1 uræmia 1 hæmorrhage
Av. period of survival after perforation	29 days (range, from few hours to 68 days)
Postmortem findings:	
Heart weight	Av. 489 g. 6 cases above normal of 330 g.
Old infarction	Only 2 definite
New infarction	7 involving left ventricle and septum
Site of I.V.S. perforation	6 lower septum, 1 upper septum
Size of I.V.S. perforation	0·8–4 cm. diameter
Size of arterial obstruction	Variable

Discussion

Incidence of Septal Infarction and Rupture

Myocardial infarction often encroaches on the septum. Series only partly supported by necropsy confirmation depend on E.C.G. findings which are open to different interpretation. On available necropsy material, the incidence of septal involvement may be as high as 90%, with 30% showing massive septal infarction (Osher and Wolff 1953), but septal rupture rather than mere infarction is uncommon. Edmondson and Hoxie (1942) could collect only 13 cases (1·5%) in a series of 864 necropsies on patients with unhealed myocardial infarcts. Septal rupture is found in about 60% of cases of death due to cardiac rupture (Oblath et al. 1952). Though septal infarction is fairly common, septal rupture is relatively rare. Survival from such a rupture—even for short periods—is not often reported. Reviews of I.V.S. perforation include those of Sanders et al. (1956) and Sahagun and Burns (1956); and small series and isolated case-reports are often published—e.g., Goldman (1959) and Swithinbank (1959). But the total number of reported cases of survival, even for a few hours, after septal rupture is probably still less than 200.

Treatment and Prognosis

The prognosis in myocardial infarction with septal rupture is poor: 50% of patients die in the first week (Sanders et al. 1956) as against 11·5% in an unselected series with myocardial infarction alone (Bland and White 1941). Of the present group of 7 patients, however, only 2 died in the first week. The longest survival was sixty-eight days, and the average survival twenty-nine. Long-term survival is quite exceptional: patients who have lived four years (Zucker et al. 1952), five years (Wood and Livezey 1942), and 1 who was alive after six and a half years (Schlappi and Landale 1954) have been recorded. Progressive congestive cardiac failure is the rule in survivors; and death from this is usually not long delayed, though routine medical treatment may be of temporary value. With advances in surgical and anæsthetic techniques, surgical treatment will be increasingly feasible. There is already a report by Cooley et al. (1957) of a patient who survived six weeks after such an operation; and at necropsy the perforation was found to have been well repaired, with a small recurrent defect.

Symptoms and Signs

Bond et al. (1953) state that septal rupture associated with cardiac infarction can occur at any age, but that the average age of recorded cases is the same as that of uncomplicated cardiac infarction—i.e., 61. This tallies well with the present series where the average age at death was 64. Perforation of the I.V.S. is very uncommon under 50; and it affects twice as many men as women. Of the present series, 5 were men. In most of the reported cases of perforation complicating acute myocardial infarction the patient's condition suddenly became worse, usually in the first ten days after the original infarction. Surprisingly

enough, only 2 of the present 7 cases showed any sudden change in symptoms. All perforations occurred, however, in the first two weeks after infarction, and 6 out of 7 in the first week.

The full clinical picture is easy to recognise. A patient with recent myocardial infarction is found to deteriorate, often with symptoms suggesting further infarction; commonly chest pain recurs with associated dyspnœa. The patient is shocked and hypotensive, and may show rhythm changes; an apical systolic thrill is commonly found. On auscultation, a loud pansystolic murmur is heard over the whole precordium, but especially at the left lower border of the sternum; this murmur is reduced in intensity if the blood-pressure is low. The second pulmonary sound may be accentuated. Signs of congestive cardiac failure quickly develop, but acute pulmonary œdema due to left ventricular failure is reported to be uncommon. Of the patients in this series, 6 had congestive cardiac failure, and in 2 of these left ventricular failure developed later.

Electrocardiographic Changes

The diagnosis of I.V.S. rupture may be impossible to confirm by routine methods during life. Nevertheless, E.C.G. changes may be of great help, at least in giving evidence of septal infarction. Osher and Wolff (1953) reviewed the E.C.G. and pathological findings in 35 cases of myocardial infarction.

The hearts were examined by the Schlesinger method of injection-plus-dissection, supplemented by multiple microscopic sections of the myocardium. They found that conduction defects were diagnostic of septal infarction (1) when bundle-branch block or high-grade atrioventricular block appeared following myocardial infarction (2) when complete right bundle-branch block was associated with conspicuous Q waves in the right precordial leads or left bundle-branch block was found with left precordial Q waves and (3) when left bundle-branch block occurred with low voltage in limb and left precordial leads. QS deflections with abnormally elevated RST segments in right precordial leads without bundle-branch block suggested septal infarction. A further characteristic of septal infarction was simultaneous anteroseptal and posterior infarction, though this was rare. Evidence of anterior together with posterior infarction indirectly suggested septal involvement.

Abrahams (1957) claimed that T inversion in CR_4 with variable T inversion of CR_1 and CR_7 in the absence of Q or RST changes is evidence of restricted septal infarction. As other criteria have been suggested—e.g., Myers et al. (1949)—it is clearly impossible as yet to define the exact E.C.G. changes of septal infarction.

The E.C.G. tracings of the 7 patients in this series are reproduced in fig. 1. There is no evidence that septal perforation alters the E.C.G. pattern of septal infarction.

Confirmation by Catheter Studies

Only by cardiac catheterisation can the diagnosis of septal rupture be proved rather than presumed. In the case of Muller et al. (1950), such proof was obtained. The patient survived fifteen months; and necropsy confirmed the presence of septal rupture. Sanders et al. (1956), however, cited a case where catheterisation was unhelpful.

Differential Diagnosis

As Sahagun and Burns (1956) suggest, differential diagnosis is limited. Only a handful of conditions associated with acute myocardial infarction might give rise to confusion; of these, pericardial friction rub and functional mitral incompetence should not present undue diagnostic difficulties.

Rupture of a papillary muscle may however, simulate I.V.S. rupture: Askey (1950) found that, in 27 out of 29 reported cases, papillary rupture complicated cardiac infarction. The murmur may be either systolic, diastolic, or both, though the murmur of ruptured I.V.S. is almost invariably purely systolic. Should there be a diastolic murmur in the presence of septal perforation, it is usually due to coincidental pre-existing left ventricular aneurysm (Zucker et al. 1952, Scherf and Brooks 1949). Moreover, in cases with ruptured papillary muscle, there is sudden collapse with acute left ventricular failure, and the systolic murmur is never loud enough to give rise to a palpable thrill. This is in contrast to acute septal perforation where a thrill is common, where the development of complications may be insidious, and where congestive cardiac failure is much commoner than left ventricular failure. An intraventricular thrombus, appearing after acute cardiac infarction, may mimic the physical signs of ruptured I.V.S. (Loeper et al. 1940), but this complication is probably even rarer than rupture of a papillary muscle. Other conditions, such as pre-existing ventricular septal defect, ventricular septal defect after bacterial endocarditis, rupture of a sinus of Valsalva, rupture of aortic cusps, and rupture of chordæ tendineæ, are not associated with acute myocardial infarction, though certain of their features may resemble those of septal perforation following myocardial infarction.

Predisposing Factors

Septal infarction is not uncommon, occurring in 70–90% of cases of acute myocardial infarction, and septal rupture might be expected to take place more often than it does. Mallory and White (1939) showed that, during the first week after infarction, there is muscle necrosis and round-cell infiltration; removal of necrotic tissue and replacement by connective tissue predominate over the next five weeks. Rupture of the heart is commonest in the first week. Presumably, speed and effectiveness of repair depend on the blood-supply that is reaching the infarcted area. The I.V.S. is supplied anteriorly by perforating branches from the anterior descending coronary artery, and posteriorly by perforating branches from the right. This double blood-supply is probably one of the reasons why septal rupture is relatively rare: anastomotic channels may grow out quickly into the infarcted area from the unaffected coronary artery and promote healing, rather than necrotic breakdown.

Edmondson and Hoxie (1942) reviewed the effect of hypertension on cardiac rupture in acute myocardial infarction, and found that persistence of hypertension after infarction made for a poor prognosis, while hypertrophy or previous scarring of the heart appeared to offer some protection against rupture. In the present series, 3 patients had diastolic pressures of 110 mm. Hg or over after infarction and before perforation; 2 patients showed definite evidence of old infarction. Infarction need not be of full thickness to lead to rupture (Wessler et al. 1952, Oblath et al. 1952); shearing stresses may tear a partially infarcted muscle. Such stresses are apparently greater in the ventricular walls than in the septum, which may be another reason why rupture outwards is commoner than across the septum. Pressure gradients across myocardial muscle are also important: since the septum is partially splinted by the right ventricular pressure against the high left ventricular pressure, the gradient across the septum is less than across the ventricular walls. The series of Wessler et al. (1952) underlines these points: of 19 ruptures associated with acute myocardial infarction, all were of the left

ventricle; but only 5 were septal, the remaining 14 rupturing into the pericardial sac.

Pressor Agents and Anticoagulant Therapy

Do routine methods of treatment influence the chances of cardiac, and especially septal, rupture? Since pressure in the left ventricle may exert a great influence it follows that hypotension should protect from rupture. Similarly, overenthusiastic use of pressor agents in the first few days after acute myocardial infarction might materially increase the risk of rupture, as this is the period before adequate repair has taken place. Lange and Aarseth (1958) published a somewhat disturbing report on a carefully controlled series of 141 patients with acute cardiac infarction, half of whom received anticoagulants: the incidence of spontaneous rupture in those patients was twice that in the controls. Honey and Truelove (1957) showed, however, that patients with myocardial infarctions who do not receive anticoagulant treatment run a greater risk of dying from thromboembolic phenomena, such as pulmonary infarctions. Only 1 patient in the present series was given anticoagulants after the infarction and before perforation of the I.V.S.

Conclusion

Survival after septal perforation following cardiac infarction may not be so uncommon. With advances in techniques, surgery of this condition may become feasible. Accurate diagnosis will, therefore, assume greater practical importance.

Summary

7 cases are described in which rupture of the interventricular septum followed acute myocardial infarction.

6 of these cases were diagnosed during life.

A plea is made for early accurate recognition of this not so uncommon condition.

My thanks are due to Dr. J. R. Bolton, Dr. Donald Hunter, Dr. J. M. Ledingham, and Dr. A. L. Wyman for allowing me to discuss their patients, and to the various pathologists who conducted the postmortem examinations. I am particularly grateful to Dr. A. L. Wyman for his encouragement with this paper. Of the 7 patients here described, I saw only cases 3, 4, 5, and 7, all of whom were under Dr. Wyman's care. I also thank the electrocardiographers and photographic technicians of the various hospitals where the patients were treated; I should especially like to acknowledge the help of Mr. Raymond Ruddick, of The London Hospital photographic department.

REFERENCES

Abrahams, D. G. (1957) *Brit. Heart J.* **19,** 233.
Askey, J. M. (1950) *Amer. J. Med.* **9,** 528.
Bland, E. F., White, P. D. (1941) *J. Amer. med. Ass.* **117,** 1171.
Bond, V. F., Welfare, C. R., Lide, T. N., McMillan, R. L. (1953) *Ann. intern. Med.* **38,** 706.
Brunn, F. (1923) *Wien. Arch. inn. Med.* **6,** 533.
Cooley, D. A., Belmonte, B. A., Zeis, L. B., Schnur, S. (1957) *Surgery,* **41,** 930.
Edmondson, H. A., Hoxie, H. J. (1942) *Amer. Heart J.* **24,** 719.
Galt, H. (1909) *Lancet,* i, 161.
Goldman, K. P. (1959) *Brit. J. clin. Pract.* **13,** 651.
Honey, G. E., Truelove, S. C. (1957) *Lancet,* i, 1155.
Lange, H. F., Aarseth, S. (1958) *Amer. Heart J.* **56,** 257.
Latham, P. M. (1845) Lectures on Diseases of the Heart. London.
Loeper, M., Varaya, A., Lesobre, R., Lesourd, M. (1940) *Arch. Mal. Cœur,* **33,** 237.
Mallory G. K., White, P. D. (1939) *Amer. Heart J.* **18,** 647.
Malone, R. G. S., Parkes, W. E. (1955) *Brit. Heart J.* **17,** 448.
Muller, O., Humerfelt, S., Rasmussen, H., Storstein, O. (1950) *Acta cardiol., Brux.* **5,** 633.
Myers, G. B., Klein, H. A., Hiratzka, T. (1949) *Amer. Heart J.* **37,** 720.
Oblath, R. W., Levinson, D. C., Griffith, G. C. (1952) *J. Amer. med. Ass.* **149,** 1276.
Osher, H. L., Wolff, L. (1953) *Amer. Heart. J.* **45,** 429.
Sahagun, E., Burns, R. O. (1956) *Ann. intern. Med.* **44,** 657.
Sanders, R. J., Kern, W. H., Blount, S. G. (1956) *Amer. Heart J.* **51,** 736.
Scherf, D., Brooks, A. M. (1949) *Amer. J. med. Sci.* **218,** 389.
Schlappi, J. C., Landale, D. G. (1954) *Amer. Heart J.* **47,** 432.
Swithinbank, J. M. (1959) *Brit. Heart J.* **21,** 562.
Wessler, S., Zoll, P. M., Schlesinger, M. J. (1952) *Circulation,* **6,** 334.
Wood, F. C., Livezey, M. M. (1942) *Amer. Heart J.* **24,** 807.
Zucker, R., Leibowitz, S., Brody, H., Sussman, R. M. (1952) *Arch. intern. Med.* **89,** 899.

TYPE-3 ADENOVIRUS INFECTION

T. M. BELL
B.Sc. Glasg.
LECTURER IN BACTERIOLOGY

GRACE TURNER
M.B. Aberd.
TRAINEE ASSISTANT

A. MACDONALD
M.A., M.D. Aberd.
PROFESSOR OF BACTERIOLOGY IN THE UNIVERSITY OF ABERDEEN

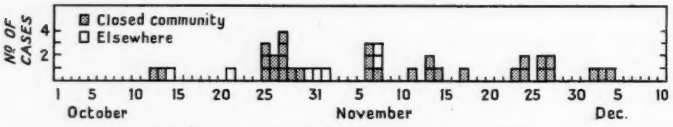
D. A. HAMILTON
M.B. Aberd.
GENERAL PRACTITIONER, AUCHINBLAE

CLINICAL differentiation of virus infections of the upper respiratory tract is notoriously difficult, and only occasionally, as in the diagnosis of influenza, are laboratory investigations considered likely to be rewarding. This is an understandable view in infections which are often mild, of short duration, and unaffected by treatment. The recognition of an increasing number of new respiratory agents may lead to a better understanding of these infections; but, temporarily at least, the doctor's difficulties remain since ætiological relations have still to be firmly established, and we know little about their incidence. Certain members of the adenovirus group of agents should escape these general criticisms, for a few of them are known to cause recognisable illnesses which have been studied in several countries.

Infection with the type-3 adenovirus in children of school age is often described as pharyngoconjunctival fever—a useful name but one which does not suggest the wider range of symptoms which may occur, as in the present outbreak. In this as in other areas adenovirus infections caused by types 1 and 2 are often unrecognised infections of young children, or single sporadic cases, whereas localised outbreaks of clinical disease are usually caused by other serological types, such as types 3 and 8. There were many cases of type-3 infection in English schools in 1955 (Kendall et al. 1957), and in this area the last known outbreak, caused by type 8 (Bennett et al. 1957), was in 1956. Such a long interval between outbreaks of clinical infection does not help familiarity, and there is also need for more rapid means of laboratory confirmation if the adenovirus infections are to be recognised more often and removed from the mass of undifferentiated febrile catarrhs or influenza-like illnesses.

Clinical Details

From Oct. 13 to Dec. 4, 1959, thirty-nine cases of acute febrile illness were seen in a rural practice, and of these thirty-two were in a community of ninety-five boys aged 8–13 years. The ill boys complained of headache, dizziness, photophobia, and, in many cases, stuffed nose or sore throat. Temperatures ranged from 99° to 104°F, with usually an M-shaped curve, and most of the boys were flushed during the first rise. Most also had back, limb, and neck stiffness, but only one child had positive Kernig and Brudzinski signs. The expected cervical adenitis was not a prominent feature. Many of the boys had obvious pharyngitis, while several complained of earache and a few developed bullæ on the eardrums. Definite conjunctivitis was noted in only two cases. Six either vomited or had gastrointestinal symptoms, and most complained of nausea. The illness usually lasted about 5 days, and all made a complete recovery without treatment other than rest in bed. The figure shows the onset of illness of cases within the community, and in those seen outside. The incubation period was thought to be about 7–8 days, but it was not possible to determine the means of spread of the infection either within the community or among children outside. There was no possibility of spread from a swimming-pool. It seemed likely that the infection



Type-3 adenovirus infection in a rural practice.

required close personal contact by an agent which was not highly infectious. Seven sporadic cases were seen outwith the community.

Laboratory Investigations

Since the cases were some distance from the laboratory, throat and eye swabs and sample of fæces were sent by post. These were examined for bacterial pathogens as well as for viruses. Acute and convalescent samples of blood were collected, usually with an interval of 25 days.

For attempted virus isolation two types of tissue-culture cells—(1) HeLa cells, or (2) human embryonic kidney and liver cells, or human amnion—were used routinely. A standard series of media was used for culturing all four types of cells. They contained lactalbumin hydrolysate 0·5%, calf serum 2%, 10%, or 20%, and Hanks' BSS together with the usual antibiotics. Cell suspensions were prepared using trypsin 0·25%, and after growth two tubes of each cell line were inoculated with the supernatant fluid from a 20% suspension of fæces or fluid from extracted eye or throat swabs. After incubation at 37°C the tubes were examined daily and compared with controls.

Isolated viruses which had the general characteristics of the adenovirus group were typed by neutralisation with type-specific antisera prepared in our laboratory with prototype strains obtained from Dr. H. G. Pereira. Sera against types 1–11 and 14 were used, two tubes per type with the usual controls. Acute and convalescent samples of serum from patients were tested both for complement-fixing and neutralising antibodies. Two antigens prepared against the prototype-3 virus and a type-3 strain isolated during the outbreak were used for complement-fixation tests which were done in plastic plates by standard methods (World Health Organisation 1959). Neutralisation tests with all sera were also performed by standard methods against a strain isolated during the outbreak and also against prototype strains 1, 3, 4, 7, 10, and 14. The suspensions of virus for serological tests were grown in human embryonic liver cells.

Results

Because specimens from the cases were obtained at various stages during the outbreak the laboratory findings were thought to sample the infection throughout its course. From twelve boys, 11 samples of fæces, 5 throat swabs, and 1 conjunctival swab were examined. Blood samples were taken from five cases at 25 days' interval, and from two others at 2 months; from one patient only a convalescent sample was received.

At the beginning of the outbreak Coxsackie-B5 virus was isolated from one boy, and a fourfold rise of neutralising antibody was demonstrated in his serum. The possibility that other boys in the outbreak could be similarly infected was excluded both by failure to isolate any other Coxsackie virus, and by negative serological tests, in the eight cases examined.

All other viruses isolated during the outbreak proved to be type-3 adenovirus. The 1 conjunctival swab was positive, and 4 out of 5 throat swabs, and 10 out of 11 fæcal specimens were also positive. Type-3 adenovirus was thus isolated from about a third of the cases during the outbreak, and, apart from the single instance of Coxsackie B5, no other virus or bacterial pathogen.

HeLa cells are usually recommended for the isolation of adenoviruses, but in several laboratories difficulty has been experienced in maintaining these cells in continuous culture over a long period, and, which may be more important, in maintaining them in a state of full sensitivity, suitable for recovery of adenovirus. We were thus interested to know not only if our own routine strain of HeLa cells was an effective tissue for this purpose but also to compare it with other tissue-culture cells at our disposal. As we were not able to use all four types of tissue culture for each of the original isolations a 20% suspension of fæces from cases was stored at −20°C for further tests. One specimen arrived in the laboratory 10 days after collection when virus had already been isolated from the same patient, and this specimen was subsequently left at 4°C for 2 months before the suspension was prepared (no. 7 in table I). It was thus possible to examine all four tissue cells simultaneously using aliquots of the inoculum for each pair of tubes of the different tissues. Only fæcal specimens could be tested in this way, for there was not enough material from throat or conjunctival swabs. The results, in italics, in table I show the time taken in days for the original isolation in the particular tissue found to be first positive. The other figures show the direct comparison of the four tissues under identical conditions. All tubes were examined daily and the time was reckoned from the day on which at least one of a pair of tubes showed complete and typical degeneration.

TABLE I—TIME REQUIRED (DAYS) FOR DEMONSTRATION OF TYPE-3 ADENOVIRUS IN FÆCES

No. of specimen	Tissue culture			
	HeLa	Human amnion	Human embryonic kidney	Human embryonic liver
1	8	8	5	3 (*3*)
2	8	4	5	2 (*7*)
3	9	9	5 (*6*)	3
4	7	7	3 (*5*)	2
5	5	7	3 (*3*)	2
6	9 (*7*)	9	6	3
7	16	17	7	7
8	7	6 (*7*)	4	3
9	11	13 (*8*)	7	4
10	6	5	3 (*4*)	2
Mean isolation time	9·6	9·7	5·3	3·6

From table I it is clear that both human embryonic kidney and liver cells provided more rapid evidence of adenovirus infection and that the strain of HeLa cells employed was not appreciably better than human amnion cells for this purpose. Many factors may influence the rapidity of isolation of adenovirus, including the size of inoculum (which in this case was not known), the type and strain of tissue cells, and the composition of the media used to grow and maintain the cells. From experience of several lines of HeLa cells the one in use at this time was thought to be of about average sensitivity, but Grayson et al. (1958) have emphasised the variability of such cells. There was no difference between the four tissues in the number of viruses isolated—the differences being confined to the time taken for isolation.

The demonstration of a rising titre of antibody for the type of virus isolated during the course of illness does not prove that virus and illness are causally related, but it is valuable evidence. The serological tests shown in table II were done with a strain of type-3 virus isolated during the outbreak, and also with the prototype-3 strain. Neutralisation tests were also performed on all samples of serum against prototype 1, 4, 7, 10, and 14

TABLE II—COMPLEMENT FIXING AND NEUTRALISING ANTIBODIES IN CASES EXCRETING TYPE-3 ADENOVIRUS

Case	Complement fixation with		Neutralisation of	
	Prototype 3	Outbreak 3	Prototype 3	Outbreak 3
1	N.D.	<4/32	<5/40	<5/40
2	<4/128	<4/128	<5/20	<5/20
3	<4/128	<4/128	<5/20	<5/20
4	8/64	8/64	<5/80	<5/80
5	<4/16	<4/32	<5/20	<5/40
6	<4/32	<4/64	<5/80	<5/80
7	<4/8	<4/16	<5/40	<5/40

4/32 = Acute/convalescent serum antibodies; N.D. = not done.

viruses. Minor heterotypic rises of antibody were obtained with all of these types, except type 1, and there was no evidence that any of them was concerned in the outbreak.

These results show that infection with type-3 virus occurred when the boys had their symptoms, and together with the results of virus isolation they strengthen the view that this was the cause of illness. Proof of the ætiological significance of isolated viruses in a particular adenovirus disease also requires statistical correlation, and in this outbreak only a third of the boys was investigated. Nevertheless epidemiological features of the infection, and the failure to isolate any bacterial pathogen or any other virus apart from the single strain of Coxsackie B5, are all consistent with the other evidence showing that the outbreak was caused by type-3 adenovirus.

Discussion

The name pharyngoconjunctival fever was given by Bell et al. (1955), and has been familiar for outbreaks of type-3 adenovirus infection, particularly in schoolchildren. Types 7 and 14 adenoviruses have also been found to cause a similar illness. The main clinical features of this disease are fever, pharyngitis, rhinitis, conjunctivitis, and enlarged cervical lymph-nodes. Of the cases described by Kendall et al. (1957) more than 70% complained of sore throat and headache, 97% had enlarged cervical lymph-nodes, and all serologically proved, as distinct from clinical cases, had conjunctivitis. In the present outbreak of type-3 infection conjunctivitis was noted in only four of the thirty-two cases, and the virus was isolated from the only eye swab sent for examination. Ginsberg et al. (1955) have also described an outbreak in which there were no obvious signs of conjunctivitis.

Another difference from the usual clinical picture was the common complaint of stiffness in the back, legs, and neck, and this was also found by Forssell et al. (1956) and by Barr et al. (1958) in Sweden. Lumbar puncture was performed in eight of the latter series of cases, but with negative findings. It was realised that painful cervical lymph-nodes might cause neck stiffness, but this could not account for the stiffness in back or legs. Several workers have noticed that gastrointestinal symptoms may occur, and six of the present thirty-two cases either vomited or had abdominal symptoms, while most complained of nausea. Clearly it might be misleading if pharyngoconjunctival fever was to be considered the only manifestation of outbreaks of type-3 adenovirus infection, and until more is known it would be wise to think of the triad of symptoms as indicating one of a possible range of clinical syndromes in schoolchildren.

The isolation of adenovirus is often considered fairly simple, and primary explant cultures of human amnion, human respiratory tissues, or serially progagated cell cultures such as HeLa cells have been recommended (World Health Organisation 1959). HeLa cells have been most widely used, but Grayson et al. (1958) have found that some 20% of adenoviruses from clinical material required 15–33 days for isolation. They also demonstrated that different laboratory lines of HeLa cells varied in their sensitivity to adenovirus; using one line only 9 type-4 adenoviruses were recovered, while with a second line 17 adenoviruses were isolated from the same clinical specimens. Contamination of stock HeLa cells with pleuropneumonia-like organisms is common, and this must also be considered. Several different lines of HeLa cells have been used in this laboratory, and the strain employed in the present investigation was thought to be of average sensitivity. It is known that the composition of the culture media for these cells affects the quantity of virus produced, and we have used calf-serum which is believed to contain inhibitors against adenoviruses. We were, however, unable to show that such inhibitors appreciably affected the rapidity of isolation of type-3 adenoviruses. Using the same growth and maintenance medium for HeLa, human amnion, and human embryonic kidney, and the same maintenance medium for liver cells we found a consistently more rapid rate of isolation from all the types of clinical material tested with the two human embryonic tissues.

It is usually recommended that for adenovirus recovery it may be necessary to incubate tissue cultures for up to a month, or alternatively to make several blind passages of culture fluids at short intervals. In the present investigation it was necessary to do this only when attempting to isolate virus from some of the throat swabs. While such procedures are necessary when the amount of virus in clinical material is very small, it is also desirable to try to ensure that the virus is propagated on as sensitive tissue cells and possible.

Summary

In a community of ninety-five boys thirty-two developed symptoms suggestive of pharyngoconjunctival fever, except that conjunctivitis was rare and muscular stiffness was common. Type-3 adenovirus was isolated from eleven boys, and seven of them showed confirmatory rises in complement-fixing and neutralising antibodies.

Type-3 adenovirus was isolated more quickly by using human embryonic tissue-cultures than with a strain of HeLa cells.

We wish to thank Miss Helen Martin for technical help.

REFERENCES

Barr, J., Kjellen, L., Svedmyr, A. (1958) *Acta pædiat., Stockh.* **47**, 365.
Bell, J. A., Rowe, W. P., Engler, J. L., Parrott, R. H., Huebner, R. L. (1955) *J. Amer. med. Ass.* **128**, 997.
Bennett, F. M., Law, B. B., Hamilton, W., MacDonald, A. (1957) *Lancet*, ii, 670.
Forssell, P., Lapinleimu, K., Strandström, H., Oker-Blom, N. (1956) *Ann. Med. exp. Fenn.* **34**, 287.
Ginsberg, H. S., Gold, E., Jordan, W. S., Katz, S., Badger, G. F., Dingle, J. H. (1955) *Amer. J. publ. Hlth*, **45**, 915.
Grayson, J. T., Loosli, C. G., Smith, M., McCarthy, M. A., Johnston, P. B. (1958) *J. infect. Dis.* **103**, 75.
Kendall, E. J. C., Riddle, R. W., Tuck, H. A., Rodan, K. S., Andrews, B. E., McDonald, J. C. (1957) *Brit. med. J.* ii, 131.
World Health Organisation (Expert Committee on Respiratory Viruses) (1959) *Tech. Rep. Wld Hlth Org.* no. 170, 1st report, p. 26.

A LEUCINE-SENSITIVE INSULIN-SECRETING TUMOUR

DAVID MARRACK
M.D. Lond.
SENIOR LECTURER IN CHEMICAL PATHOLOGY,
THE NATIONAL HOSPITAL, QUEEN SQUARE, LONDON, W.C.1

VINCENT MARKS
B.M. Oxon., M.R.C.P.E.
M.R.C. CLINICAL RESEARCH FELLOW IN CHEMICAL PATHOLOGY,
KING'S COLLEGE HOSPITAL, LONDON, S.E.5

F. CLIFFORD ROSE
M.B. Lond., M.R.C.P.
FIRST ASSISTANT IN THE DEPARTMENT OF NEUROLOGY,
ST. GEORGE'S HOSPITAL, LONDON, S.W.1

Cochrane et al. (1956) reported the induction of hypoglycæmia as an abnormal response to *l*-leucine given by mouth to three children and an adult. An increase in insulin-like activity of plasma after *l*-leucine administration has been demonstrated in *l*-leucine-sensitive children but not in normal children (Di George et al. 1960, Grumbach and Kaplan 1960, Mabry et al. 1960). Butter-

field et al. (1960) present evidence that *l*-leucine-induced hypoglycæmia in an adult " is due to a *transient* rise in plasma-insulin activity " (our italics). The response to *l*-leucine given by mouth in one of three adults with insulin-secreting pancreatic tumours whom we studied, lends support to this suggestion.

Our three patients had been repeatedly observed to have low blood-glucose levels associated with episodes of disturbed consciousness, disorientation, incoordinated movements, and occasionally coma, and these symptoms were rapidly relieved by glucose intravenously. All three cases gave a positive response to the glucagon test—i.e., initial hyperglycæmia followed by profound hypoglycæmia after intramuscular injection (Marks 1960)—and to the tolbutamide test in which a precipitate and prolonged lowering of blood-glucose follows intravenous injection (Marrack 1961).

Only one case showed a precipitate fall of blood-glucose when fed with *l*-leucine (0·1 g. per kg. body-weight). This patient went into hypoglycæmic coma with convulsions, which had to be relieved by glucose intravenously 30 minutes after the ingestion of *l*-leucine. Blood taken from a limb vein whilst the surgeon was manipulating the tumour, and the tumour itself, both had a very high plasma-insulin content (by radio-chromato-electrophoretic immuno-assay). After removal of the tumour this patient had no further clinical attacks of hypoglycæmia, and blood-glucose levels were within the normal range. When the oral leucine test was repeated after operation the blood-glucose level did not drop, and there was no detectable clinical change.

Discussion

The presence of an insulin-secreting tumour cannot be excluded because hypoglycæmia is precipitated when *l*-leucine is given by mouth. Schwartz et al. (1958) reported the precipitation of hypoglycæmia by *l*-leucine in two adults who were later found to have pancreatic islet-cell tumours. One of these had an islet-cell carcinoma with metastases, and the leucine sensitivity persisted after operation. A case of islet-cell adenoma similarly examined by Monro (1960) was not leucine-sensitive.

The probability is that in our patient before operation oral *l*-leucine initiated the release of extra insulin from the tumour. But if this is so there must be at least two biochemical mechanisms by which insulin can be released, since in only one of our three cases was the tumour stimulated by leucine.

The rat's blood-glucose level normally falls after *l*-leucine administration (Cochrane 1960). In essential leucine sensitivity of children there seems to be a genetically determined abnormality which gives them an additional mechanism for activating the release of insulin. Presumably a similar biochemical mechanism may be acquired by the abnormal cells of some insulin-secreting tumours.

After rapid intravenous injection of insulin or tolbutamide, hypoglycæmia does not appear in less than 25 minutes. The time-interval between oral administration of leucine and the appearance of hypoglycæmia in sensitive individuals suggests that only part of the insoluble *l*-leucine can have been absorbed before the insulin-releasing mechanism is activated. Such a view is consistent with the observations of Woolf (1960) and of Cochrane (1960).

Di George et al. (1960) said: " It is not known whether this net increase in insulin produced by leucine represents accelerated synthesis or decreased breakdown ". The evidence from our patient suggests that the increase in plasma-insulin arises from accelerated insulin release rather than from accelerated insulin synthesis, and this is incompatible with the concept of decreased insulin breakdown in sensitive subjects.

Conclusions

In a patient of any age the finding that *l*-leucine induces hypoglycæmia does not exclude the presence of an insulin-secreting tumour. A positive response to the glucagon and tolbutamide tests is strongly in favour of an insulin-secreting tumour, whereas evidence of familial hypoglycæmia favours essential leucine sensitivity.

Hypoglycæmia induced by *l*-leucine in sensitive individuals seems to be due to accelerated insulin release rather than to increased synthesis or decreased breakdown.

We are grateful to Dr. Ellis Samols, of the department of medicine, Royal Free Hospital, London, W.C.1, for the plasma-insulin assays.

REFERENCES

Butterfield, W. J. H., Whichelow, M. J., Wright, P. H., Woolf, L. I. (1960) *Nature, Lond.* **188,** 70.
Cochrane, W. A. (1960) *A.M.A. J. Dis. Child.* **99,** 476.
— Payne, W. W., Simpkiss, M. J., Woolf, L. I. (1956) *J. clin. Invest.* **35,** 411.
Di George, A. M., Auerbach, V. H., Mabray, C. C. (1960) *A.M.A. J. Dis. Child.* **100,** 543.
Grumbach, M. M., Kaplan, S. L. (1960) *J. Pediat.* **57,** 346.
Mabry, C. C., Di George, A. M., Auerbach, V. H. (1960) *ibid.* pp. 526, 529.
Marks, V. (1960) *Brit. med. J.* i, 1539.
Marrack, D. (1961) To be published.
Monro, R. S. (1960) *Post Grad. med. J.* **36,** 160.
Schwartz, T. B., Flanagan, G. G., Stuppy, G. W., Tarum, D. W. (1958) *J. Lab. clin. Med.* **54,** 944.
Woolf, L. I. (1960) *Clin. chim. acta,* **5,** 327.

Preliminary Communication

AN 11 β-HYDROXYLASE INHIBITOR IN THE TREATMENT OF RESISTANT ASCITES

2-METHYL-1, 2-bis(3-pyridyl)-1-propanone-ditartrate (Su-4885), a synthetic analogue of amphenone B, selectively inhibits 11 β-hydroxylation of adrenal steroid precursors [1 2] and therefore presumably inhibits aldosterone production. Amphenone has been used as an aldosterone antagonist but was finally abandoned because of its untoward side-effects.[3] Su-4885 and its hydrochloride, Su-8874 (' Metopirone '), are considerably less toxic and might therefore be considered as diuretics. We have assessed metopirone as a diuretic, alone and in combination with chlorothiazide and spironolactone, in two patients with cirrhosis and resistant ascites.

THE STUDY

The patients were a 52-year-old man and a 36-year-old woman with cirrhosis of unknown ætiology. Ascites had been present for at least 12 months before treatment, and paracenteses had been necessary.

They each excreted in the urine less sodium than 1 mEq. per 24 hours during a control period of 3 days on a constant 22 mEq. dietary intake (see figs. 1 and 2), and this did not increase when chlorothiazide 2 g. daily was given. The first patient was also resistant to the combination of chlorothiazide 2 g. daily, spironolactone 400 mg. daily, and mannitol 2 litres of 10% solution intravenously. After a further control period of 3 days, both patients started prednisone 5 mg. twice daily.

1. Chart, J. J., Sheppard, H., Allen, M. J., Bencze, W. L., Gaunt, R. *Experientia,* 1958, **14,** 151.
2. Liddle, G. W., Island, D., Lance, E. M., Harris, A. P. *J. clin. Endocrin.* 1958, **18,** 906.
3. Hertz, R., Pittman, J. A., Graff, M. M. *ibid.* 1956, **16,** 705.

Their urinary sodium and clinical status did not change, and after 3 days metopirone (900 mg. t.d.s.) was added. After 4 days the first patient showed no increase in urinary sodium, and the second showed a very slight increase to 5 mEq. per 24 hours. In both patients the clinical state was unchanged.

When chlorothiazide was added in a dosage of 2 g. daily, both patients began to lose weight and their urinary sodium excretion increased. The first patient's sodium diuresis was slow, reaching 40 mEq. daily, but after the addition of two mannitol infusions the sodium excretion increased to 110 mEq. per day. He then lost weight steadily, passing 60–70 mEq. of sodium daily for 3 weeks. This continued during 32 days of metopirone therapy, there being no sign of resistance to the drug. In the second patient metopirone caused a sodium excretion of 75–100 mEq. daily for 2 weeks.

At this stage spironolactone (600 mg. per day in the first patient and 400 mg. per day in the second) was added to the combination. A dramatic increase in sodium excretion was seen, reaching a peak of 175 mEq. per day in the first patient and 290 mEq. per day in the second, and body-weight decreased dramatically. The first patient required potassium supplements after 2 weeks' chlorothiazide and metopirone therapy, as the serum-potassium level had fallen to 2·4 mEq. per litre. The second patient was given potassium supplements throughout.

After 3 days' combined treatment metopirone was stopped and the patients continued on spironolactone, chlorothiazide, and prednisone. The 24-hour urinary sodium excretion fell in both patients to the levels obtained with metopirone without spironolactone, and the urinary sodium excretion was not further reduced when the prednisone was stopped.

Neither patient showed any side-effects from continuous metopirone therapy, and clinical evidence of adrenal insufficiency was not seen when prednisone therapy was stopped. Both patients showed considerable clinical improvement with clearance of their ascites, the weight-loss averaging 20 kg., and both patients' serum-albumin levels rose from less than 2·6 g. to more than 3·5 g. per 100 ml.

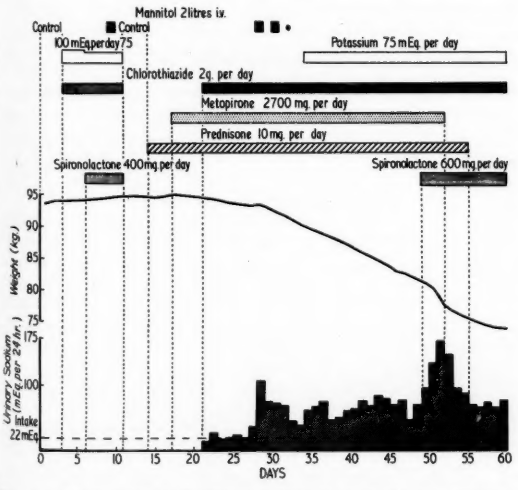


Fig. 1—A 52-year-old man with cryptogenic cirrhosis and intractable ascites requiring repeated paracenteses over 12 months.

The patient was completely resistant to chlorothiazide alone or in combination with spironolactone 400 mg. per day, and mannitol 2 litres 10% intravenously. He showed no response to prednisone and metopirone, but with the addition of chlorothiazide he finally began to lose weight and to excrete sodium. Mannitol considerably potentiated this diuresis, but after 2 weeks he required potassium supplements to control hypokalæmia. The addition of spironolactone 600 mg. per day produced a dramatic loss of weight and of urinary sodium which quickly reverted to previous levels on the withdrawal of metopirone from the combination. The patient was not resistant to the increased dose of spironolactone when combined with chlorothiazide.

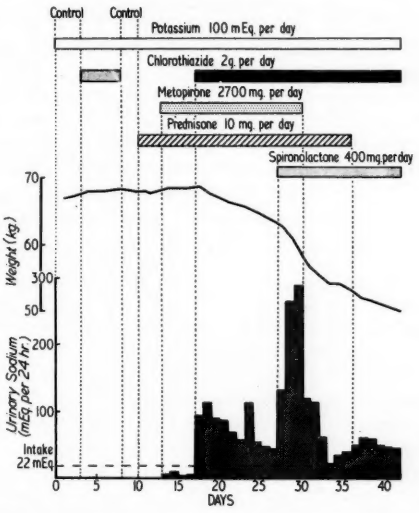


Fig. 2—A 36-year-old woman with cryptogenic cirrhosis and resistant ascites.

The patient was completely resistant to chlorothiazide alone, and showed only a small sodium diuresis when given prednisone and metopirone. The addition of chlorothiazide caused a steady weight-losing sodium diuresis which was even further potentiated by the addition of spironolactone 400 mg. per day. The withdrawal of metopirone resulted in a fall in urinary sodium excretion to previous levels. The patient responded less dramatically to spironolactone and chlorothiazide than to metopirone and chlorothiazide. Prednisone withdrawal did not affect the sodium diuresis.

DISCUSSION

Metopirone alone caused a slight urinary sodium increase in one patient, and no change in the other. It was therefore clear that, like the other aldosterone antagonist spironolactone,[4] an additional diuretic, such as chlorothiazide, acting on the proximal tubule was necessary to promote diuresis.

Metopirone inhibits 11 β-hydroxylation in adrenal steroid biosynthesis and so prevents the formation of 11-oxycorticoids (cortisol, corticosterone, and aldosterone). The precursor of cortisol, 11-desoxy-17-hydrocorticosterone (compound S), and the precursor of corticosterone, 11-desoxycorticosterone (DOCA) therefore accumulate. The fall in circulating cortisol and corticosterone releases the anterior pituitary gland from its normal feedback control mechanism and increased corticotrophin secretion follows. This results in further increased adrenal synthesis of the 11-desoxycorticosteroid precursors which are ineffective in suppressing corticotrophin production.[5,6] This explains the necessity of giving prednisone with metopirone as a substitute for cortisol so that corticotrophin secretion is not increased and the 11-desoxy precursors do not accumulate.

Aldosterone secretion is probably not under the control of corticotrophin,[7] and it would therefore not be affected by prednisone administration. Patients retaining fluid

4. Shaldon, S., McLaren, J. R., Sherlock, S. *Lancet*, 1960, i, 609.
5. Bissel, G. W., Scott, A. L., Farnsworth, W. E., Winkler, I. *N.Y. St. J. Med.* 1959, **59**, 3596.
6. Liddle, G. W., Herschel, L. E., Kendall, J. W., Williams, W. C., Townes, A. W. *J. clin. Endocrin.* 1959, **19**, 875.
7. Farrell, G. *Physiol. Rev.* 1958, **38**, 709.

have a stimulus to aldosterone secretion, and if this continued when metopirone was given, one would theoretically expect that the 11-desoxycorticoid precursors of aldosterone would accumulate (this is a theoretical consideration as the 11-desoxycorticoid precursor of aldosterone has not yet been isolated). The continued effectiveness of metopirone therapy suggests either that these substances are not potent salt-retaining steroids or, alternatively, that the stimulus to aldosterone secretion has diminished, although this is unlikely as the plasma-volume in these patients decreased.

The dramatic potentiation of sodium diuresis when spironolactone was combined with metopirone was most unexpected. Spironolactone does not affect adrenal synthesis nor the release of aldosterone, and it is presumed to act by inhibiting the action of aldosterone on the distal renal tubule.[8 9] Thus it is difficult to explain its action in the presence of effective inhibition of the synthesis of aldosterone by metopirone. Three explanations are possible:

1. When metopirone therapy is prolonged, aldosterone secretion is not effectively inhibited. This seems unlikely as the drug did not produce diuretic resistance.

2. Spironolactone is not an aldosterone antagonist but it blocks an alternative pathway of sodium reabsorption in the distal tubule. This again seems unlikely because spironolactone is known to antagonise infused aldosterone in adrenalectomised animals [10 11] and in patients with Addison's disease.[12]

3. The secretion of the 11-desoxy aldosterone precursor was increased in these patients as they underwent diuresis. This substance might not be sufficiently sodium-retaining to allow resistance to metopirone to show but yet be sufficiently active to be blocked by spironolactone, a peripheral aldosterone antagonist. Increased diuresis would therefore ensue.

The last explanation is the most attractive, and analysis of urine from these patients may allow isolation of the 11-desoxy precursor of aldosterone. Further work is in progress to test these hypotheses.

SUMMARY

Metopirone is an 11 β-hydroxylase inhibitor which presumably prevents the production of aldosterone by the adrenal gland. When used with chlorothiazide, it increased urinary sodium excretion in two patients with cirrhosis and ascites. Addition of spironolactone, an antagonist of aldosterone at the renal tubular level, potentiated this diuresis.

We should like to thank Messrs. G. D. Searle for financial assistance, and the Medical Research Council for a maintenance grant to J. R. McLaren. We should also like to thank Dr. A. K. Pittman, of Ciba Laboratories, Ltd., for supplies of 'Metopirone'.

STANLEY SHALDON
M.A., M.B. Cantab., M.R.C.P.
JANET R. MCLAREN
B.SC. Melb.
Department of Medicine, Royal Free Hospital, London, W.C.1

8. Wiggins, R. A., Hutchin, M. E., Carbonne, J. W., Doolan, P. D. *Proc. Soc. exp. Biol., N.Y.* 1959, **100**, 1625.
9. Wilde, W. S., Malvin, R. L., Sullivan, L. P., Vander, J. A. Program of the American College of Physicians Fortieth Annual Session; p. 80. Chicago, 1959.
10. Kagawa, C. M., Cella, J. A., van Arman, C. G. *Science*, 1957, **126**, 1015.
11. Slater, J. D. H., Moxham, A., Hurter, R., Nabarro, J. D. N. *Lancet*, 1959, ii, 931.
12. Liddle, G. W. *Science*, 1957, **126**, 1016.

Reviews of Books

A Clinical Prospect of the Cancer Problem: Neoplastic Diseases at Various Sites

Introductory Volume. Editor: D. W. SMITHERS, M.D., F.R.C.P., F.F.R., professor of radiotherapy in the University of London. London: E. & S. Livingstone. 1960. Pp. 232. 37*s.* 6*d.*

THE quotation at the start of this book neatly introduces its purpose: "To explode a myth is accordingly not to deny the facts but to re-allocate them." The myth is that something called "cancer" exists; and the facts that are reallocated are those concerning tissue development, senescence, injury, isolation from control, and clinical observation. The word "cancer" is usually applied to an assortment of phenomena, so ill-defined that to group them into one narrow category serves no useful purpose. Indeed, to do so is misleading, for it gives rise to the idea that the phenomena has some unique characteristic not possessed by "non-cancer". The whole concept of the "malignant cell" is wrong. Neoplasms, "benign" or "malignant", are better defined as belonging to a category of phenomena within the larger group of tissue maldevelopments and malformations, and arbitrarily defined by certain characteristics of behaviour, not of assumed cellular uniqueness. Malformations due to arrest of development come at one end of the scale which passes through those due to differential susceptibility to injury or ageing to hyperplasia and neoplasia. "The degree of variation from normal behaviour patterns changes continuously along a scale, with a tendency to independent progression of each characteristic, towards complete escape from control. The word cancer vaguely covers the most disorganised of these tissue malformations, being applied according to individual preference on the basis of a selection of these degrees of change in several characteristics which are expected to give rise to the greatest danger to the life of the organism. Since the meaning of this word can have no precise boundaries this side death, it would be better if we were to abandon its use in communications having some pretence to scientific reporting."

The closely reasoned argument ranges widely over the many special branches of study associated with the investigation of neoplasia. The viewpoint is, however, that of the clinician; and there could be no better place to get the right perspective, for the investigation of neoplasm is the investigation of individuals. For too long the main emphasis of research has been on the mythical "cancer cell", trying to find out why it is "cancerous" and how to kill it. Chemotherapy research requires, in Professor Smithers' view, much firmer clinical direction into channels where it has a chance of being effective by the correction of particular abnormalities of function or by restoring the lost organisation of tissues.

If this view of the problems of neoplasia is accepted (and it seems far more rational than its competitors), it is more profitable to think in terms of neoplasms of various tissues than of neoplasia in general. Carcinoma of the lung and carcinoma of the bladder have some common characteristics and justify being placed in a single group of "carcinomas"; but they differ widely in most other characteristics, because the one is a malformation of the lung and the other of the bladder. This admirable book is the introduction of a series of volumes on neoplastic diseases at various sites, two of which, on the lung and bladder, have already been published. It is a stimulating work.

Diseases of the Nervous System in Infancy, Childhood and Adolescence (4th ed. Oxford: Blackwell Scientific Publications. Springfield, Ill.: Charles C. Thomas. 1960. Pp. 1548. £11 16*s.*).—Dr. Frank R. Ford's book needs little introduction, and this edition retains the indispensable qualities of its predecessors. New concepts of neurology in infancy may cause the whole subject to be rewritten, but until that day Ford stands alone for authority, comprehensiveness, and style. Although revision has been extensive, some recent work of importance has not found a place—notably in the areas of genetics, and the treatment of congenital malformations and acute infections of the central nervous system.

THE LANCET

LONDON 17 DECEMBER 1960

Cardiac Arrest and Resuscitation

DANGEROUS cardiac inaction is due to one of three distinct conditions—complete heart-block, ventricular fibrillation, or asystolic arrest.[1 2] Two of these three conditions are now readily treatable. Heart-block can be overcome by administering isoprenaline,[3] or better by stimulating the ventricular muscle.[4 5] Ventricular fibrillation [2] can be stopped by passing through the heart a depolarising current of sufficient magnitude, voltages of 150-250 being usual. Even asystolic arrest will, in some cases, yield to so-called cardiac massage—an inaccurate term, better replaced by " cardiac pumping " [6] or " intermittent cardiac compression ".

CALLAGHAN and BIGELOW [7] sparked off the present interest in the treatment of heart-block by artificial pacemaking, and later HOPPS and BIGELOW [1] applied their researches to the needs of cardiac surgery—particularly to the treatment of accidental damage to the bundle of His, which is such a hazard in the repair of ventricular septal defects. Direct electrical stimulation of the ventricles to produce pulse-rates exceeding idioventricular rhythm is now accepted by all cardiosurgical centres, and attention is centred mainly on the most suitable way of achieving this. The most widely practised method is that of WEIRICH et al.[8] in which the negative electrode is placed in the subcutaneous tissues or the muscles of the precordial region. By means of voltages varying from 0·5 to 10, and currents of about 5 milliamps, pulses at the required rate, usually lasting not more than 2 milliseconds, can produce cardiac contraction at a pre-set rate, this being empirically determined by what is considered normal for the individual under given circumstances. Such a method of stimulation usually works well; and the indications for stimulation are steadily increasing. But long-continued stimulation of the heart [9]—for instance, in postoperative heart-block and in Stokes-Adams attacks—presents difficulties. Infection along the electrode tracks cannot be warded off for ever. Moreover the presence of electrically active foreign bodies in the myocardium eventually leads to fibrosis, and this in turn increases the electrical resistance of the tissues through which the current passes; consequently the stimulating voltages have to be gradually increased too. And the need for a thoracotomy, and therefore for a thoracic surgical team, somewhat limits the availability of cardiac pacemaking.

The myocardium can be stimulated through the intact skin by electrical induction,[10] or even by radiofrequency [11 12]—a development which spurs the imagination to the treatment of heart-block in outer space. Both these methods, and also the implantation of transistorised miniature stimulating units [13 14] in the body wall, require preliminary thoracotomy—an operation of some magnitude in patients not usually very fit. In this country WEALE [15] has shown that experimental pacemaking can satisfactorily be achieved by stimulating the ventricles by an electrode passed through a peripheral vein into the right ventricle; and FURMAN and ROBINSON [16] in the U.S.A. have applied this method successfully to two patients. By this means thoractomy and myocardial fibrosis are both circumvented—and electrodes are at all times exchangeable. But, whereas the patient with an implanted transistorised pacemaker may be mobile and may theoretically need no attention for anything from four weeks [13] to ten years,[14] the patient with an electrode in the ventricles suffers some loss of mobility. The introduction of an electrode into the myocardium via a cannula inserted through the chest wall [9 17] has the same drawback, and vigilance is needed to avert cardiac tamponade. With implanted transistorised pacemakers, stimulating voltages cannot be increased when electrical resistance has risen; and the patient should probably not stray too far from medical supervision.

Attempts to correlate the rate of ventricular stimulation with changing physiological demands, such as standing or exercise, have led to the experimental introduction of pacemakers " triggered " [18] by the electrical changes in the atria, which in heart-block have no chance of influencing ventricular rate and, indirectly, cardiac output. The P wave can be monitored from either the atrial surfaces or the cavities. As with untriggered pacemakers, both the transthoracic [19] and the venous-catheter [20] techniques are being explored. It cannot be long before their clinical application will be reported, though evaluation of the advantages of " triggered " pacemakers over the ones at present in use promises to be a cardiological nicety. It is claimed that " triggering " may increase cardiac output by some 15%—a figure conceivably of important marginal value.

MCMILLAN [2] has shown that ventricular fibrillation is best treated by thoracotomy, not only because defibrillating apparatus is designed only for intrathoracic use, but also because sometimes ventricular fibrillation cannot be distinguished from asystolic arrest unless the heart is rapidly exposed to the surgeon's eye.[21] This operation has a success-rate of only 24% under operating-theatre conditions; and, outside the operating-theatre, " penknife " thoracotomy has yielded a most discourag-

1. Hopps, J. A., Bigelow, W. G. *Surgery*, 1954, **36**, 833.
2. McMillan, I. K. R. *Brit. med. Bull.* 1955, **11**, 229.
3. Lillehei, C. W. *J. thorac. Surg.* 1957, **33**, 57.
4. Nightingale, A., Weale, F. E. *Guy's Hosp. Rep.* 1960, **109**, 147.
5. Weale, F. E., Deuchar, D. C., Nightingale, A. *ibid.* p. 157.
6. Stahlgren, L. H., Angelchik, J. *J. Amer. med. Ass.* 1960, **174**, 226.
7. Callaghan, J. C., Bigelow, W. G. *Ann. Surg.* 1951, **134**, 8.
8. Weirich, W. L., Gott, V. L., Lillehei, C. W. *Surg. Forum*, 1958, **8**, 360.
9. Thevenet, A., Hodges, P. C., Lillehei, C. W. *Dis. Chest*, 1958, **34**, 621.
10. Abrams, L. D., Hudson, W. A., Lightwood, R. *Lancet*, 1960, i, 1372.
11. Glenn, W. W. L., Mauro, A., Longo, E., Lavietes, P. H., Mackay, F. *New Engl. J. Med.* 1959, **261**, 948.
12. Leatham, A., Robinson, B., Siddons, H., Davies, J. G. *Lancet*, July 2, 1960, p. 49.
13. Senning, A. *J. thorac. Surg.* 1959, **38**, 639.
14. Chardack, W. W., Gage, A. A., Greatbatch, W. *Surgery*, 1960, **48**, 643.
15. Weale, F. E. *Lancet*, 1959, ii, 73.
16. Furman, S., Robinson, G. *Surg. Forum*, 1958, **9**, 245.
17. Ross, J. K., Harkins, G. A. *Lancet*, 1959, ii, 1109.
18. Stephenson, S. E., Jr., Edwards, W. H., Jolly, P. C., Scott, H. W., Jr. *J. thorac. Surg.* 1959, **38**, 604.
19. Folkman, M. J., Watkins, E. *Surg. Forum*, 1958, **8**, 331.
20. Battye, C. K., Weale, F. E. *Thorax*, 1960, **15**, 177.
21. Milstein, B. B. *Ann. R. Coll. Surg. Engl.* 1956, **19**, 69.

ing success-rate.[6] When facilities for observation are exceptionally good—for example, when the patient is being observed electrocardiographically [22]—the situation is somewhat different. Here defibrillation may be achieved by a catheter electrode,[1 15] or by direct cardiac puncture of the ventricular cavity and the passage of defibrillating shocks through an insulated needle with a bare tip. Provided such equipment is kept ready, a therapeutic test need take only a few seconds before thoracotomy and intermittent manual compression are initiated.

Asystolic arrest is thus the remaining hurdle. WOODWARD [23] has found that sometimes the heart-beat is restored by immediately elevating the limbs, which fills the arrested heart with blood; but the main method of treatment is still direct manual compression coupled with intracardiac injection of adrenaline or calcium chloride.

Iron-retention Diseases

HÆMOCHROMATOSIS in the form of "bronzed diabetes" is well known, though uncommon, in Europe and America. It is thought to be caused by slightly increased absorption of dietary iron, amounting to about 3–5 mg. daily throughout life.[24] In South Africa excessive iron in the tissues of the Bantu population was first noted some years ago; and examination of tissues from patients who had died in hospital or accidentally suggested that the prevalence of such siderosis lies between 40% and 88%. The amounts of iron have varied from a slight excess to a deposition as severe as in idiopathic hæmochromatosis. This state of affairs has been explained in two different ways. J. and T. GILLMAN [25] considered that the siderosis was caused by a widespread metabolic defect associated with chronic malnutrition; whereas WALKER and ARVIDSSON [26] believed that it was caused by excessive iron intake, because the Bantu cook their food and prepare their beer in iron cooking-vessels. The two schools also differed about the pathological changes in the liver. The GILLMANS thought that iron was first deposited in the liver cells themselves, whereas WALKER's group thought the reticuloendothelial cells were first involved. BOTHWELL and BRADLOW [27] have reinvestigated this problem by examining tissue from Bantus who had died accidentally; they studied the histopathological changes in the liver and, in some cases, the spleen, and they estimated the amount of iron in the tissues.

BOTHWELL and BRADLOW studied the livers of 147 patients and the spleens of 50; most of the patients were aged 20–50, and only 16 were females. The iron concentration in the liver exceeded the normal maximum of 0·1% in all except 16; and the concentration tended to rise with age, reaching a maximum at 40–50 when the average iron concentration was as much as 1·10%. Some degree of siderosis of the liver was found in 89% of the patients; in 59% it was mild (i.e., not more than 1·0%, which is a concentration of the same order as that in idiopathic hæmochromatosis). Histological studies showed quite clearly that the hæmosiderin granules were deposited first in the liver cells, and appeared in the Kupffer reticuloendothelial cells only when the higher concentrations of iron were present. Portal fibrosis developed only when the iron concentration was really high; of 40 subjects with iron concentrations between 0·50 and 1·99% only 8 had mild portal fibrosis, and in 1 it was assessed as moderate. But the 11 patients with iron concentrations above 2% all had portal fibrosis; in 2 this was mild, in 5 moderate, and in 2 severe; in 2 there was frank cirrhosis. Investigation of the spleens showed that the iron concentrations paralleled those in the liver.

These results support the opinion of the GILLMANS, which is linked with the observation that a similar distribution of iron in the liver is found in animals fed on deficient diets with considerable added iron.[28] The appearances are quite different from those caused by iron accumulations following hæmolysis or infection; in these circumstances it is the reticuloendothelial cells that take up most of the iron.[29] But BOTHWELL and BRADLOW cite an investigation which suggests that the diet of the Bantu in Johannesburg, though not optimal, is not in fact gravely deficient in any of the main constituents and is certainly not comparable to the laboratory animals' diet of uncooked corn meal. Among the Bantu iron intake is undoubtedly excessive, often exceeding 100 mg. a day, and the average serum-iron level in Bantu males is about twice that in white males. On the other hand, it has proved very difficult to produce cirrhosis of the liver in animals by overloading the tissues with iron; and since recent investigations and the features of idiopathic hæmochromatosis suggest that portal fibrosis depends on the iron exceeding a minimum concentration, some additional factor must be needed. Chronic malnutrition does not seem to be a sufficient explanation, nor does variation in the ratio of iron and phosphorus in the diet. A different explanation has been proposed by GOLBERG and SMITH.[30]

When rats are given excessive amounts of iron by parenteral injection, iron accumulates in the liver and other tissues, but no hepatic cirrhosis is found even after so large a stretch of a rat's life as two years. GOLBERG and SMITH found that when such iron overloading was combined with oral administration of the antimetabolite DL-ethionine, or with a diet poor in protein and vitamin E, hepatic cirrhosis appeared within a few weeks. They think that the mechanism of the siderosis is "primarily one of excessive iron-binding in the liver, from which the increased intestinal absorption follows secondarily". And they point out that in these conditions, unassociated with hæmolysis or marrow aplasia, the common factor is "actual or potential liver damage, the latter taking the form of

22. Bishop, C., Honey, M., Taylor, D. G. *Brit. med. J.* July 16, 1960, p. 191.
23. Woodward, W. W. *Lancet*, Nov. 19, 1960, p. 1120.
24. Granick, S. *Bull. N.Y. Acad. Med.* 1949, **25**, 403.
25. Gillman, J., Gillman, T. Perspectives in Human Nutrition. New York, 1951.
26. Walker, A. R. P., Arvidsson, U. B. *Trans. R. Soc. trop. Med. Hyg.* 1953, **47**, 536.
27. Bothwell, T. H., Bradlow, B. A. *Arch. Path.* 1960, **70**, 279.
28. Gillman, T., Hathorn, M., Canham, P. D. *Amer. J. Path.* 1959, **35**, 349.
29. Heilmeyer, L., Keiderling, W., Wöhler, F. *German med. Monthly*, 1959, **4**, 111.
30. Golberg, L., Smith, J. P. *Amer. J. Path.* 1960, **36**, 125.

disordered metabolism of the hepatic cell". They suggest that such liver damage involves the excessive production of an iron-binding material which they call "haptosiderin", and which may be similar to the copper-binding polypeptide isolated from the liver in Wilson's disease. This explanation would reconcile the hypotheses of GILLMAN and of WALKER and their co-workers since the disordered hepatic metabolism postulated by GILLMAN would be responsible for the excessive iron uptake from the undue amount of iron in the diet noted by WALKER. GOLBERG and SMITH believe that the low protein content of the Bantu diet may be the responsible factor; the survey in Johannesburg indicated that the average daily intake of animal protein was 25 g. and of vegetable protein 39 g., which is certainly less than the usually recommended daily minimum of 80–100 g. protein. Other deficiencies may be revealed by further work on this syndrome.

Annotations

DIURETICS

THE observations that the sulphonamides were potentially diuretic [1] eventually led to the production of potent diuretics such as the chlorothiazides. Their widespread use in the past two years or so has underlined their value in the management of œdema and has also enhanced our understanding of kidney function. These advances in knowledge have been assembled in a special issue of *Chemotherapia* [2] in honour of the recent Basle International Congress of Internal Medicine at which œdema was discussed.

The benzothiadiazine group of diuretics probably affect sodium excretion in the proximal tubule and potassium excretion in the distal tubule, and some support for this is afforded by the studies of Darmady and of Gaunt et al.[3] on the selective localisation of radioactive hydrochlorothiazide in these areas. The mechanism of tubular interference is ill-understood, but the effect on sodium and potassium excretion determines their main advantage and disadvantage. To displace the prototype, new diuretics acting in this manner should be expected to cause increased sodium excretion with diminished potassium excretion. Thus far, none of the growing family of chlorothiazide analogues has a significant advantage; instead, commercial competition has led to such small refinements as the incorporation of potassium; but the dose of potassium chosen by the pharmaceutical company may be too small. When long-term diuretic therapy is necessary, and particularly when the underlying cause of œdema is hepatic cirrhosis, adequate oral potassium supplements are essential. This is effectively and palatably administered in an effervescent tablet containing potassium bicarbonate, potassium acid tartrate, and anhydrous citric acid, as devised by Hadgraft [4] at the Royal Free Hospital. Each tablet contains about 6·5 mEq. of potassium and is equivalent to 0·5 g. of potassium chloride; a dose of 8 tablets daily is recommended for cirrhotic patients on a low-sodium diet.[5]

1. Schwartz, W. B. *New Engl. J. Med.* 1949, **240**, 173.
2. Rentchnick, P. *Chemotherapia*, 1960, **1**, 225.
3. Gaunt, R., Renzi, A. A., Chart, J. J. *ibid.* p. 238.
4. Hadgraft, J. W. *Pharm. J.* 1960, **184**, 277.
5. Sherlock, S. *Practitioner*, 1960, **185**, 492.

Hypokalæmia is but one of the undesirable consequences of effective diuretic therapy; others include hypochloræmic alkalosis, low serum-electrolytes, hyperuricæmia, hyperglycæmia, and rashes and thrombocytopenia.[6] The development of hyperglycæmia and glycosuria due to these sulphonamide-type diuretics is somewhat unexpected since another family of sulphonamides has precisely the opposite effect. Goldner et al.[7] have shown that this complication is restricted to diabetics and prediabetics.

When œdema is associated with hyperaldosteronism, administration of the aldosterone-antagonising steroid, spironolactone, has a potent diuretic effect by acting on the distal tubule. The use of spironolactone together with chlorothiazide has proved a synergistic combination in cirrhotic patients with ascites resistant to either diuretic alone.[8] Shaldon [9] has reviewed his experience of the management of fluid retention in 51 cirrhotic patients in the past eighteen months, in which spironolactone has been available for clinical trial. 33 (65%) patients responded to a low-sodium diet and either a mercurial or chlorothiazide-type diuretic, and 18 (35%) also needed spironolactone. Only 4 (8%) patients had no satisfactory diuresis, and these subsequently died of liver failure. His recommended diuretic regimen for patients with hepatic cirrhosis is initially rigid dietary salt restriction and bed rest; if this is insufficient one of the chlorothiazides and potassium are given. If thiazide therapy has not produced satisfactory diuresis in a week, spironolactone is added and potassium supplements are reduced. Satisfactory diuresis usually starts within three days and continues at a slow steady rate. Uninterrupted combined diuretic therapy may be necessary for some months to eliminate ascites, and thereafter it is continued indefinitely. Finally, if the patient fails to respond to this combination, it may be worth administering an osmotic diuretic—intravenous mannitol—in an effort to initiate diuresis. This carefully planned regimen has virtually eliminated resistant ascites, repeated abdominal paracenteses, and the use of Southey's tubes; but close supervision is imperative if electrolyte disturbances and hepatic coma are to be avoided.

Since the choice of diuretic was last discussed in these columns,[10] spironolactone, which then appeared promising, has become freely available and its value has been firmly established. Its widespread and indiscriminate use may, however, lead to some disappointing results and to criticism of its lack of efficacy in certain œdematous states. This can be expected if aldosterone antagonists are administered where œdema is principally due to factors other than hyperaldosteronism. Some patients with congestive cardiac failure, for instance, do not secrete aldosterone in excess [11]; and it has been suggested that urinary aldosterone levels are normal in "left-sided" heart-failure whereas they are elevated in "right-sided" heart-failure.[12] Spironolactone will be used more rationally when a technique has been devised for detecting more readily cases with hyperaldosteronism.

To this means of peripheral blockade of aldosterone are now being added central inhibitors of aldosterone secretion. One such substance—methbipyrapone or SU4885—selectively inhibits the 11β-hydroxylation of steroids in

6. Veygrat, R. *Chemotherapia*, 1960, **1**, 327.
7. Goldner, M. G., Zorowitz, H., Akgun, S. *New Engl. J. Med.* 1960, **262**, 403.
8. Shaldon, S., McLaren, J. R., Sherlock, S. *Lancet*, 1960, i, 609.
9. Shaldon, S. *Proc. R. Soc. Med.* (in the press).
10. *Lancet*, 1959, ii, 279.
11. Laragh, J. H. *in* The Clinical Use of Aldosterone Antagonists (edited by F. C. Bartter); p. 49. Oxford, 1960.
12. Wolff, H. P., Koczorek, K. R., Buchborn, E. *Lancet*, 1957, ii, 63.

the adrenal cortex, and so reduces secretion of the three main corticoids—aldosterone, corticosterone, and cortisol.[3 13] Liddle [14] observed no significant differences between this central inhibitor of aldosterone secretion and a peripherally acting spirolactone in the urinary output of sodium and potassium in a healthy subject maintained on a constant high-sodium diet and prednisolone. On p. 1330 of this issue, Dr. Shaldon and Miss McLaren report their preliminary observations of the use of the hydrochloride of methbipyrapone—metopirone (Su-8874)—also a central inhibitor of aldosterone secretion, in 2 cirrhotic patients. Both had longstanding ascites which had proved resistant to various conventional treatments. Metopirone alone caused slightly increased urinary sodium levels in 1 but not in the other; and the clinical state of both patients remained unchanged. The addition of chlorothiazide promoted diuresis, indicating that it behaves synergistically with metopirone (a central inhibitor) as well as with spironolactone (a peripheral antagonist of aldosterone). On theoretical grounds, it could be predicted that spironolactone would be ineffective if aldosterone production were being blocked by metopirone, and Shaldon and McLaren do not explain why they used this seemingly incompatible mixture. Nonetheless, spironolactone was added to the combination of metopirone and chlorothiazide with quite dramatic and unexpected potentiation of sodium diuresis. But perhaps even more important are the theoretical implications of these findings. The 11-desoxycorticoid precursor of aldosterone has not yet been isolated, but if it accumulates as a result of metopirone blockade, then possibly it is antagonised by spironolactone. Although some of its properties can be surmised according to this hypothesis, the next essential step is to endeavour to isolate it.

THE OXFORD CLINICAL SCHOOL

IN its Michaelmas number, the *Oxford Medical School Gazette* (always a lively publication) has a symposium on the future of the Oxford clinical school. This shows again the difficulty of breaking a tradition—in this case the tradition that the Oxford preclinical student leaves the rarefied atmosphere of Oxford for "a little Smithfield Market atmosphere, or the like". In writing of the present problems of the school the five Nuffield professors suggest that the biggest difficulty is that there are not enough students and that their calibre is not high enough. This difficulty has persisted even though the school, which is already well established in graduate teaching and research, offers the student excellent facilities—facilities so good, indeed, that the Goodenough Committee suggested that its role should be to turn out consultants, investigators, and teachers. The professors believe not only in what they can give to the students but also in what the students can give to them, and they find unthinkable any suggestion that the whole scheme should be abandoned—after so much money and effort have been invested in it.

The number of clinical students from Oxford would increase if the Oxford preclinical teachers did not remain, for the most part, ignorant of what goes on in the teaching hospital some quarter of a mile from their laboratories. And the number of clinical students from elsewhere might increase if the Oxford clinical school advertised more skilfully in other preclinical schools—not excluding Cambridge. But the difficulty of finding the right candidates for medicine is something which all face alike. Most teachers agree that, of their more talented science pupils, the proportion choosing a medical career is now lower than in the years immediately after the war. The propaganda of *Ward 10* may encourage patients to entrust themselves to our care, but will hardly induce clever young men and women to become doctors. If some of the medical information given through television, sound broadcasting, newspapers, popular lectures, and the like could emphasise not only the human side of medicine but also the scientific satisfaction to be derived from it, then more of the most able minds might be attracted to the profession.

WATER

To judge from his report for 1959 Dr. I. Gordon, medical officer of health for Ilford, would have found himself among kindred souls at the recent UNESCO conference on the problems of the arid lands. The borough draws its water partly from the Metropolitan Water Board and partly from the South Essex Water Company. Even in 1959 the first gave almost all that was asked, but the supplies from the latter were at times so insufficient that even the school privies could not be flushed. No-one seems to have died of thirst, but 25 gallons per head per diem is not really enough. The S.E.W.C. does not expect much improvement for several years. It has some large engineering projects in hand, but the amount of water which it draws from the M.W.B. cannot be increased until 1968 and it is still uncertain whether it will get permission to abstract more water from an unnamed river. (Essex is not so rich in purling brooks as to make this puzzle very difficult.) The M.O.H. is cross (and we do not blame him for it) because the S.E.W.C. did not foresee the shortage, has no representative of his authority on its board, provides no annual report, and seems to have rather old-fashioned ideas on public relations. The privately owned statutory water companies are some of the most efficient utilities in the land, but efficiency at any level is no excuse for failing to win the public confidence. Those who enjoy a monopoly must take the lead in exorcising the popular image of a suffering "we" and an omnipotent "they".

The fundamental worry of all suppliers of water in the London basin is that it is one of the driest parts of England and for more than sixty years the level of the water table in the surrounding chalk has been falling. The M.W.B. makes up its supplies from springs and wells in Hertfordshire and Kent and by drawing on the Thames. The S.E.W.C. serves a less favoured area without any great river and must do its best in a country notorious for brackish waters. At the same time the demand continues to increase. There are not only more people but also more bathrooms. Industry is insatiable, and we are sure the time has come when some more pressure should be put on the more lavish users to find ways either of saving water or of re-using it after purification. Rationing by price has failed. Some thirsty businesses, such as breweries, draw from their own artesian wells, but this water comes from the same strata that supply the general public. This industrial lust for more and more water is not limited to London, and even in such places as Wales (where most visitors find water in excess) it has caused alarm and grief. Another class of users who have troubled some smaller undertakings are the dairy farmers, who often, for reasons which are almost forgotten, enjoy a supply either at a fixed

13. Coppage, W. S. Jr., Island, D., Smith, M., Liddle, G. W. *J. clin. Invest.* 1959, **38**, 2101.
14. Liddle, G. W. *in* The Clinical Use of Aldosterone Antagonists (edited by F. C. Bartter); p. 14. Oxford, 1960.

rate or free. An ample supply of clean water is a sine-qua-non for dairying; but, having only two hands, the busy farmer sometimes finds turning off the tap beyond his powers. Lastly there are those—especially in suburban districts—who wish to wash their cars and water their gardens, and for these Dr. Gordon seems to have a soft spot. We wish that we could share his sympathy, but doubt whether this class of user got much attention at the UNESCO conference.

We owe the beginnings of our admirable supplies of potable water to the sanitary awakening in the middle of the last century. Clean water meant freedom from typhoid, dysentery, and cholera; and this is still the main reason for its supply. Many industrial processes call for clean water, but relatively few for water of potable quality. If the difficulties of supply forbid a separation of "clean" and "potable" we can at least value the latter at its proper worth as one of the buttresses of our public health. When water is short we would encourage any water undertaking anywhere to forbid the use of its valuable product on the cabbage patches and to enforce this ruling with all its powers. Any number of waterbutts can be filled from the roof, and the real enthusiast can dig his own well—as many cottagers have done and some still do. And, if the gardener is too lazy for these measures, let him grow only those plants which will stand the drought as his fellows in less humid climates have done for centuries. Then the children in Ilford will be able to flush the privies.

FALLOUT IN AIR AND BONE

As far as we know, no-one has fired a high-yield nuclear weapon for over two years, and this commendable omission is probably reflected in new details [1] of radioactive fallout in air and rain. Airborne particulate radioactivity in and around this country has been sampled for some years in the lower stratosphere, in the troposphere, and at ground level; and samples of rainwater are collected at two stations for analysis of radioactivity. The data show that concentrations in air and rain of long-lived fission-product activity reached a maximum in 1959 and have since decreased significantly. How much radioactive debris thrown up by weapon testing has still to come down? Working from observations on deposition and published data on stratospheric injection, Pierson et al.[1] estimate that of a total injection of between 51 and 66 megatons equivalent fission yield, between 25 and 40 megatons remained in the stratosphere at the beginning of 1959. And about 11 megatons came down during 1959. If fallout is a simple exponential matter, these estimates point to a "common" half-residence time of one to two years—much less than was at one time supposed. The stratospheric reservoir may thus be empty quite soon.

New assays [2] of radioactive strontium in human bone in the United Kingdom in 1959 show some further increase for stillborn infants and children under 5; but in the second half of the year there was relatively little change compared with the first six months. For the whole of 1959 the average level of ^{90}Sr in bone samples from children under 5 was 3·05 $\mu\mu$C per g. of calcium (in 1958 it was 1·4). The highest single value in 1959 was 9·5 and the lowest 0·4. For adult bones the average radioactive strontium content remained a little over 0·1. The new monitoring report [2] which gives these figures records measurements made at the Woolwich Outstation of the Atomic Energy Research Establishment and in Glasgow and Cambridge; but it includes no comment on the significance of the results. That will come in the Medical Research Council's second report on radiation hazards, to be published soon.

1. Pierson, D. H., Crooks, R. N., Fisher, E. M. R. Radioactive Fallout in Air and Rain. AERE-R3358. H.M. Stationery Office. 7*s*.
2. Medical Research Council: Monitoring Report Series no. 1. Assay of Strontium-90 in Human Bone in the United Kingdom. H.M. Stationery Office. Pp. 18. 1*s*. 6*d*.

INTERTERRITORIAL MEDICINE

Dec. 1 was notable for surgeons and gynæcologists in West Africa, for on that day the West African Association of Surgeons came into being and its constitution was agreed at the inaugural meeting held at University College Hospital, Ibadan. This was attended by 37 West African doctors who are practising surgery—1 from Sierra Leone, 3 from Ghana, and the remainder from Nigeria. At the opening ceremony they were welcomed by the Governor of Western Nigeria, Sir Adesoji Aderemi, the Oni of Ife. Sir Samuel Manuwa took the chair and was later elected the first president of the Association. At the scientific sessions, continuing till Dec. 5, ten papers were read, cases were demonstrated, and a morning was occupied with operations by the hospital staff. The Premier of Western Nigeria, Chief the Hon. S. L. Akintola, held a reception for the Association, and he was also the main speaker at its first dinner. The Association of Surgeons of Great Britain and Ireland, and the corresponding Association in East Africa, were represented at the meeting. The West African Association of Surgeons is the first interterritorial body of specialists in this part of the world, and its successful start is encouraging.

INAUGURAL REPORT

THE Wolfson Foundation, which was set up in 1955 with the general aims of advancing education and health in the United Kingdom and Commonwealth, has published a report [1] of its first five years. The first three were sensibly spent in assembling an efficient administrative machine and in exploring needs, and the actual work did not begin till July, 1958. But even in this restricted period over £3,300,000 has been distributed. Of this sum almost £1,300,000 went to medical projects. Some of the grants given for new buildings include: £450,000 to provide the Royal College of Physicians of London with a larger home with more scope; £250,000 to build the Westminster Hospital a modern school of nursing; £150,000 to the Postgraduate Medical School of London for the Wolfson Institute, which will ultimately house not only lecture theatres and common rooms, but also library, museum, and laboratories; and £184,000 to the Institute of Psychiatry at the Maudsley Hospital to build lecture theatres and common rooms as the first instalment of a larger scheme.

Another series of grants has gone to help research. The British Empire Cancer Campaign is to receive £150,000 over ten years, and requests for apparatus and equipment will be met from this Wolfson fund. It has already provided a mobaltron unit to St. Thomas's Hospital, a new cobalt source to the theratron unit at Mount Vernon Hospital, and four climatic chambers for the Edinburgh animal supply and research unit. Support to individual workers includes a fellowship to Mr. A. M. H. Bennett for his studies on the application of stereotaxic

1. The Wolfson Foundation Report 1955–60. Obtainable from the director of the Trust, Lieut.-General Sir Harold Redman, 20, Copthall Avenue, London Wall, E.C.2.

techniques in cerebral surgery, and a grant to Mr. Wylie McKissock for anatomical and biochemical investigations of cerebral hæmorrhage. Medicine will also benefit from many of the Trust's educational benefactions. The work of the new institute and chair of criminology, for instance, will cover medical and social aspects of criminal behaviour, and the new university halls of residence in London and Glasgow will doubtless shelter some medical students from the harsh realities of lodging-house life.

NEW RESPIRATORY VIRUSES

RESPIRATORY infections are the commonest cause of disease, disability, and death in this country. The Newcastle upon Tyne survey [1] has again demonstrated the importance of these infections in children under 5 years. In the U.S.A. a study of 10 " healthy " young adults showed that in nine months each had on average 7 discrete minor illnesses, mostly involving the upper respiratory tract.[2] Strides have been made in determining the viral ætiology of those infections not due to bacteria. New myxoviruses (para-influenza types 1, 2, and 3) have been discovered,[3] and the role of the adenoviruses [4] has been clearly shown: on an earlier page of this issue Mr. Bell and his colleagues describe an outbreak resembling pharyngoconjunctivitis which was associated with type-3 adenovirus. There is also one other new myxovirus —S.A.[5]—that may cause respiratory disease in man. Sabin [6] has described a new group—the reoviruses —some of which cause such disease.[7] Members of the enterovirus family also cause respiratory disease; and Coe [8] virus and the newly isolated common-cold viruses [9] may prove to be members of this family, just as the JH [10] and 2060 [11] viruses probably are. In 1944 Eaton et al.[12] described the isolation of a virus from patients with primary atypical pneumonia and cold agglutinins. This finding proved difficult to confirm, and it has become evident that some outbreaks of this disease are due to *Rickettsia burneti* and that others are probably due to adenovirus infections; but in 1957 Lui [13] triumphantly vindicated Eaton's early work by reisolating the virus and demonstrating its presence in infected chick embryos by the fluorescent-antibody technique.[14] There is also another virus, originally called chimpanzee coryza agent but also called respiratory syncytial agent,[15] which is so far not classified.[16]

This virus has been shown to cause disease in man [17] but has not proved easy to isolate. Nevertheless Beem et al.[18] have isolated it from 21 of a group of 46 patients, aged 0–6 months, with respiratory illness. They used HEp 2 cells for isolation, but their success almost certainly derives from the fact that the cultures were inoculated only 1–3 hours after the specimens were collected. Specimens were not frozen, and it was subsequently found that this virus is particularly susceptible to freezing and thawing. One cycle reduced the titre, and storage at −30°C (with slow freezing) for five days destroyed the infectivity of a sample with a titre of 10^{-5} T.C.D.$_{50}$. Virus could, on the other hand, be stored satisfactorily at −50°C after being rapidly frozen at −70°C. Specimens that had yielded a respiratory syncytial virus were frozen and thawed three times to destroy this virus and were reinoculated into tissue cultures, but no additional isolations were made.

The study was performed on two groups of children (inpatients and outpatients), and in each group children with respiratory illness and controls were examined. Of 83 inpatients 27 yielded the virus, whereas of 42 controls none did. Similarly, of 85 outpatients 14 had the virus in their throats, whereas of 81 control children none did. The virus was usually isolated early in the disease. Of 23 patients tested, 16 showed a rise in complement-fixation and 14 a rise in neutralising-antibody titre in convalesence. Most of the infants in whom antibodies did not develop were under 6 months of age. Bacteriological studies failed to reveal any difference in flora between virus-positive and virus-negative cases, except that *Hæmophilus influenzæ* was isolated four times as often from virus-negative cases.

From this study it seems that respiratory syncytial virus was an important cause of respiratory illness in Chicago in the winter of 1958–59.

MORTUARIES

Medicine, Science, and the Law, the official journal of the British Academy of Forensic Science, has got away to a good start; and, judged by the first issue,[1] it will interest many besides members of the Academy.

This issue includes a paper by H. A. Sissons, delivered at the first annual meeting of the Academy, in which he demands rethinking about public mortuaries. He supports this demand by citing a letter from the Widdicombe File [2] and recounting the difficulties, and indeed dangers, confronting those who work in these places. In hospitals it may be necessary only to remind the clinicians of the teachings of Semmelweis, but in public mortuaries the operator has no sure target for his plaint. The coroner, for whom he is working, has no direct control over any mortuary and may adopt the attitude that some other person will do the work without grumbling. The local authority, which provides and staffs the mortuary, is reluctant to spend money, unnecessarily as it seems. Sissons recommends centralisation to make worth while the provision of proper facilities—a suggestion that will be widely supported. All necropsies, including those undertaken to satisfy some apparently trivial legal consideration, should be carried out with the aim of advancing knowledge. This aim cannot be pursued where indifferent operators work in unsuitable surroundings.

Dr. J. D. S. CAMERON has been elected president of the Royal College of Physicians of Edinburgh.

1. Miller, F. J. W., Court, S. D. M., Walton, W. S., Knox, E. G. Growing up in Newcastle upon Tyne. London, 1960. See *Lancet*, 1960, i, 865.
2. McNamara, M. J., Thomas, E. H., Strobl, A., Kilbourne, E. D. *Amer. Rev. resp. Dis.* 1960, **82**, 469.
3. Andrewes, C. H. *Brit. med. Bull.* 1959, **15**, 221.
4. Huebner, R. J., Rowe, W. P., Chanock, R. M. *Ann. Rev. Microbiol.* 1958, **12**, 49.
5. Schultz, E. W., Habel, K. *J. Immunol.* 1959, **82**, 274.
6. Sabin, A. B. *Science*, 1959, **130**, 1387.
7. Rosen, L., Hovis, J. F., Mastrota, F. M., Bell, J. A., Huebner, R. J. *Amer. J. Hyg.* 1960, **71**, 266.
8. Lennette, E. H., Fox, V. L., Schmidt, N. J., Culver, J. O. *ibid.* 1958, **68**, 272.
9. Tyrrell, D. A. J., Bynoe, M. L., Hitchcock, G., Pereira, H. G., Andrewes, C. H. *Lancet*, 1960, i, 235.
10. Price, W. H. *Proc. nat. Acad. Sci., Wash.* 1956, **42**, 892.
11. Mogabgab, W. J., Pelon, W. *Ann. N.Y. Acad. Sci.* 1957, **67**, 403.
12. Eaton, M. D., Meiklejohn, C., van Herick, W. *J. exp. Med.* 1944, **79**, 649.
13. Liu, C. *ibid.* 1957, **106**, 455.
14. Coons, A. H., Kaplan, M. H. *ibid.* 1950, **91**, 1.
15. Morris, J. A., Blount, R. E., Jr., Savage, R. E. *Proc. Soc. exp. Biol., N.Y.* 1956, **92**, 544.
16. Chanock, R., Roizman, B., Meyers, R. *Amer. J. Hyg.* 1957, **66**, 281.
17. Chanock, R., Finberg, L. *ibid.* p. 291.
18. Beem, M., Wright, F. H., Hamre, D., Egerer, R., Oehme, M. *New Engl. J. Med.* 1960, **263**, 523.

1. *Medicine, Science, and the Law*, October, 1960. Edited by F. E. Camps. To be published quarterly by Sweet & Maxwell, Ltd., 11, New Fetter Lane, London, E.C.4. Subscription for non-members of the Academy: 3 guineas per annum; 17*s.* 6*d.* per issue.
2. *Lancet*, 1959, ii, 1081.

Special Articles

BRITAIN AND AMERICA *

Some North Atlantic Surgical Views

FRANCIS D. MOORE
M.D. Harvard

MOSELEY PROFESSOR OF SURGERY, HARVARD MEDICAL SCHOOL; SURGEON-IN-CHIEF, PETER BENT BRIGHAM HOSPITAL, BOSTON, MASS.

TRAVELOGUES on the "American scene" have been a constant feature of British literature since the days of Captain John Smith. Since the war, there has been a resurgent outpouring of articles dealing particularly with surgery, medicine, and medical education.† To the American reader many of the features of American surgery that seem so inexplicable to the British visitor are to be explained by the differences between our two countries relative to the demand—the market—for the educational end-product: the young surgeon now ready to undertake the most expert practice, and a university post in teaching and research.

In the United States there are many communities, built within the past fifteen years, that do not have a well-organised medical establishment. In many cases they have a severe dearth of doctors and no hospital. These are not communities in the high hill coves of eastern Kentucky, where long-boned hillbilly riflemen sit around a wooden shack whittling on a stick. These are suburban communities of modern so-called "ranch-type" dwellings that embody the proverbial American standards of plenty: two chickens in every pot and two Cadillacs—or at least Volkswagens—in every garage. Many of these new communities are in the west, but they are not confined to the west. On Long Island, and in the suburban areas of Philadelphia, Baltimore, and Boston, one finds whole new developments of 10,000 to 50,000 people that have been built up where there was nothing before the war, and where any sort of medical establishment must be created out of whole cloth, or the small existing ones expanded tremendously.

It is a notorious fact—often dwelt upon by British commentators—that many surgical operations in America are done by people who are not surgeons by training or education. It is easy to assign this fact to lack of organisation, to lack of proper control and licensing, or to unvarnished avarice. Doubtless it is true that a certain fiscal attraction is revealed by the scalpel blade, yet even such self-seeking does not fully account for the American diffusion of surgical work, as one can readily satisfy oneself by making rounds at many community hospitals. There simply are not enough highly educated surgeons to go around. A study by Dr. Fred Coller (1957) showed that in some States almost 30% of the operations were performed either by general practitioners or by osteopaths. This is why there is such an urgency about our need for more medical schools and our concern over the post-graduate residency system.

In each hospital the residency system—or registrarship roster—must be as large as possible within the limit imposed by the need for each resident to have adequate personal experience. Today there are almost 15,000 Americans in residency training. This number is close to 10% of the total number of physicians who devote themselves to the care of the sick. Phrased another way, a large fraction of the American medical profession is clad in white suits, living in hospitals, receiving hopelessly inadequate fiscal support, providing care to the population—and all in the name of education.

As a result of this "seller's market" the young American surgeon finishing his residency at a good institution will have five or six attractive jobs lined up for consideration by the time he completes his hospital work. These positions may range all the way from a private group practice to an assistant professorship in a university department with opportunities for teaching and research at one of the new medical schools.

Contrast this now with the situation in Britain. A young man with a good surgical education seems to have to wait for someone else to move along before he can obtain a foothold as a consultant. According to one interpreter of the National Health Service, the need for more consultants is there but simply cannot be met because of the rigid tables of organisation set up by the N.H.S. in the teaching hospitals.

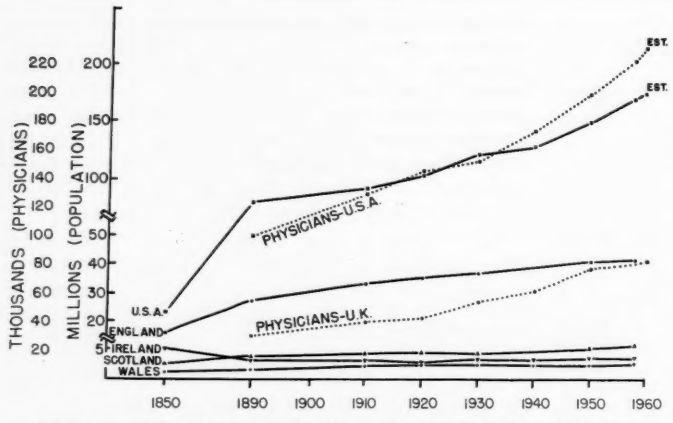
A further contrast here is of interest. I know of one of your urban teaching hospitals in which there is a surgical capacity of 140 beds. To take care of these patients there are six staff surgeons. The Brigham Hospital, in which our department is located, also has about 140 surgical beds. We have approximately twenty-five staff surgeons looking after these patients. One might say that we are overstaffed, although the balance seems to be a healthy one and gives men time to devote to teaching and investigation. There can be no question at all but that the British hospital in this instance is seriously understaffed. All six of the staff members feel this very keenly since they have but little time to deal with aspects of surgery other than operative care.

Regarding the wait for consultant posts in England, one of your deans pointed out that the great majority of new medical graduates had to go into general practice, and added: "Although the holding of a junior registrarship should be of great advantage to anyone taking up general practice it will be unfortunate if general practitioners have to be recruited from the ranks of disappointed 'trainee consultants'" (*British Medical Journal* 1950). This makes quite a contrast with the U.S.A. wherein the reverse trend is often sadly noticeable. An example is that of a man whose surgical training has been largely on the clinical side, who then finds himself in a position as chief of service at a veterans hospital or as assistant professor in some medical school wherein he wishes he knew much more about research and academic life than he actually does.

What is the reason for this difference? According to one explanation, many of the contrasts in surgical training and practice and in hospital organisation are traceable to the difference between a well-established stable population and economy in England and one that is undergoing very rapid expansion at this time in the United States. During decades when the British population was fairly stable, the number of doctors has grown at a steady rate, as is shown in the accompanying figure. Note that the slope of the curve as the number of doctors has increased

* Abstracted from the Moynihan annual lecture, University of Leeds, Sept. 24, 1959. This was the occasion of the 50th anniversary of the founding of the Moynihan Chirurgical Club.

† For reasons of length, the bibliography on transatlantic surgical visits cannot be published in full; it is available from the author.



Physicians and populations in the U.S.A. and in Great Britain and Ireland.

in Great Britain and Ireland is almost identical with the slope of increase in the United States, where, by contrast, the population has grown significantly during this time. The increasing complexity of medicine has necessitated an increase in the ratio of doctors to population. This has occurred in England; but in America the change in ratio has been continuously retarded by an increase in population growth, resulting in career opportunities of an unprecedented sort.

Postgraduate Surgical Education and Surgical Habits

In the United States we are under pressure to produce a polished surgeon at the end of his residency years—one ready to take full responsibility in his community or medical school. In most well-organised institutions our residency system has a basic tenet: that so far as possible long-term plans should be made for a man. The responsibility for the youthful surgeon must rest on one institution or be a joint responsibility between two or three institutions. The initial postgraduate commitment may be for three years, and if the resident does well he then goes on into the upper reaches of responsibility. His " chief " should remain loyal to his plans, helping to guide him through the vagaries of various clinical or research opportunities, and finally assisting him in getting a job. If the young man has any promise at all someone takes him under his wing and helps him plan.

At our hospital, as an example, the intern (house-surgeon) has a solid three-year commitment, and many of these go on to a six-year plan. One reaction of the British surgeon, on seeing such a system, is that it is stultifying, over-protective, surgical " momism " or even " popism ". " No one should stay at any hospital for that long a time." To which we would answer that these men do not remain in one hospital and that the system is therefore not stultifying. Indeed, at our hospital, again as an example, the residency involves two community hospitals and opportunities at three different urban teaching hospitals. In addition, it involves, for those who wish to take it, a one-year fellowship in the laboratory or abroad. The man emerging from it is somewhat less stultified than one who has done nothing but clinical work.

As a visitor in Britain, I am impressed with the apparent success of a contrasting system in which the young man often takes a series of unrelated posts, commonly lasting no longer than six months at any one hospital, and often involving a whole series of surgical sub-specialties before he has had general surgical operative responsibility. The Briton is apt to emphasise the length of American residency training, but for the young British surgeon who finally takes some sort of a consultancy post there has been just as long a period of education. And he is about the same age as his American counterpart. On both sides of the Atlantic the extreme extension of this training period, compounded by National Service, is a major problem.

There certainly is a pronounced difference in the degree of operative specialisation on the two sides of the Atlantic. The visiting British surgeon, travelling in America, often finds that, in his opinion, American surgeons tend to be too specialised. As one of them said: " You don't vary your work at all, you just do one field of surgery—something in the belly or something in the head—or else you don't operate at all." The Briton is apt to say: " In America you only have specialists, in Britain we have general surgeons."

There may be some truth in all this, but the visitor is prone to overlook the fact that the American surgeon, while he may be moderately specialised in what he does in the operating-room (especially if it is a feature of his own research), is apt to be a " jack-of-all-trades " and seriously over-extended scientifically in his approach to the biological sciences that underlie surgery or to other aspects of surgery with which he is concerned.

The British surgeon operates in a variety of different pathological settings and organ environments, but frequently his operations and their related visits constitute his entire clinical life. So, when the visitor states that the Americans are too specialised, he should realise that in their totality of activity through a week or a month, they may be much less specialised than their British counterparts.

Differences between the two countries, in surgical technique, have often been described. I do not think they are very impressive. Patients on both sides of the Atlantic seem to get along surprisingly well! In general the American surgeon makes a bit more fuss over the details of asepsis and is apt to be shocked by the apparently casual approach in Britain. None the less, we have our full share of the 20th-century hospital plague. We also maintain a physiological chart of the anæsthetised patient while you rarely do—an omission that often impresses us as dangerous. The Briton is much more apt to pride himself on speed than is the American surgeon. There are doubtless some American surgical habits that are unnecessarily slow. Certainly some British surgical traditions emphasise speed to the exclusion of other more worth-while objectives. Detailed methods of securing hæmostasis in open dissections are surely in contrast, but both are effective.

The differences in the objectives of the residency system have a lot to do with some of the minor differences in operative procedure. The Briton coming to America states that he is aghast to see someone taking more than an hour to do a subtotal gastrectomy. Returning home he blames it on the Halstedian system: " everyone spends all their time clamping little bleeders and frittering around

in the operating-room ". But this visitor often overlooks the fact that the man who is doing the gastrectomy may well be an assistant resident, doing his first or second case, and that, most important of all, the postoperative course of the patient is very smooth.

On the other side of the coin, we are surprised to see senior British surgeons spending a lot of their time carrying out operations on patients whose operative care we would supervise but leave in the hands of the residents. If the professor of surgery at Leland Stanford, the University of Chicago, Johns Hopkins, or Harvard spent all his time operating on the ward service patients, he could not conduct a residency training programme, because no residents would want to work for him. But, more important, he would never get anything accomplished in the way of investigation. Here again the pressure of work placed on all of you by a rather rigid table of staff organisation seems impressive to us.

The American is somewhat more prone to be concerned over the details of metabolic management of his patient and seems to have more of a desire to penetrate deeply into responsibility for the overall welfare of the patient. The Briton, somewhat more hurried by a big operating-list, is apt to leave this responsibility to others. There may be a slight difference in philosophy here as to the content of surgery itself. Certainly the American trend is increasingly toward a unified view of surgery according to which all aspects of the care of the patient are the surgeon's responsibility. I have tried to phrase our view as follows (Moore 1959):

" The surgeon employs any effective means to serve the patient best. In most instances these include an open dissection under anæsthesia, as a surgical operation, together with supportive measures based on an understanding of the patient's bodily processes in recovery . . . the responsibility of the surgeon extends into all areas of human biology so as to provide the wise and effective care which is ever the trademark of good surgery."

One of our seemingly insoluble problems is that of the so-called " vanishing ward patient ". This phrase refers to the diminution in numbers of free or charity patients in our teaching hospitals, occasioned by the growth of voluntary-hospital and surgical-insurance plans. The alleged disappearance of this ward patient places the surgeon in a difficult moral and ethical posture when he undertakes to discharge his responsibilities for post-graduate education in relation to the care of people who are, after all, private patients. This problem is a very pressing one in some centres in the U.S.A.

The reasons for this vanishing ward patient can be summarised by stating that we do not have a National Health Service or anything that approaches it, and that the growth of voluntary prepayment insurance in a period of fiscal plenty places a progressively larger fraction of our hospital population in the private and semiprivate categories. For the young man starting out in practice, this is a part of the " land of opportunity ". But for the teacher this is a real problem. Particularly is it a problem if he is trying to conduct a residency programme designed to make residents fully experienced—like Athena, fully clad from the head of some surgical Zeus. Various formulæ are being developed that permit the private surgical teaching hospital to address itself frankly to surgical care by residents for several categories of patients.

As travelling Americans not only are we surprised to see your professors and senior staff members carrying out the straightforward gastrectomies or colon resections on the ward service patients, but also we are quite envious of the volume of surgical problems that still present themselves on the wards for the care and study of the surgical staff, the registrars, and the students. Current economic trends in the United States, highly desirable in most other ways (being associated with " prosperity "), make surgical training progressively more difficult.

Most Americans who make any effort to penetrate into the administrative bureaucracy of the National Health Service are impressed with the honesty of local administration that makes it run as well as it does. American government tends to show its most seamy side in its smaller political units. It is in the city, town, and county governments that the worst grafting, racketeering, and misuse of political privilege occur. And it is in these same small local units that your National Health Service must sink or swim on the basis of the honesty of its administration and on the unbiased selection of the most competent individuals. I think I am stating accurately the sentiments of many of my countrymen when I state that the National Health Service, as you know it in England, simply could not or would not work in America because we are not set up governmentally or politically to operate a homogeneous system free of special privilege on the tremendous scale required, and with our varying local conditions.

Another interesting professional contrast between the two countries has been the growth of the great private clinics in America. No such institutions have grown up in the United Kingdom or on the Continent. The best known of these clinics are the Mayo Clinic, the Lahey Clinic, and the Cleveland or Crile Clinic. With these as prototypes, many others have sprung up over the country. In most if not all instances these clinics have been built around the professional skill, business acumen, and public-relations sense of a surgeon or surgeons. It has been the centripetal character of surgery that was responsible historically for the beginning of these clinics: one surgeon of outstanding skill in some field of work attracted referral patients from a very wide area. With occasional exceptions, these private clinics have been attended by a considerable degree of financial success, by dint of which foundations could later be established which gave these enterprises some of the aura of eleemosynary institutions. As a general rule, the most senior members of the staffs of these clinics receive somewhat less emolument than they bring into the clinic in fees, while some of the younger men find a better living than they could if they were in independent practice.

This development has seemed in some ways to be a feature of a growing country, and certainly the historically eminent position of the Mayo Clinic in relation to the great plains and the mountain West bears out such an interpretation. The surgical orientation of these clinics has always been predominantly clinical, with little emphasis on undergraduate teaching, and a considerably less emphasis on postgraduate teaching than has characterised the hospitals where the large charity teaching wards were maintained. For the British visitor who is used to seeing a very large " list " run off by each senior staff member each morning, the atmosphere at these clinics frequently appears more congenial to his past background than do the residents' operating-lists and the much more varied

activity of the charity hospitals. As a site for the study of large numbers of surgical patients managed in a uniform manner the great private clinics are unsurpassed.

The Academic Tradition

The activities of the senior surgeons and surgical teachers on the two sides of the Atlantic Ocean constitute one of the most fascinating differences between the two countries. Sir Heneage Ogilvie (1948) expressed some interesting ideas when he wrote his chapter entitled " American Surgery " in his book *Surgery, Orthodox and Heterodox*. He had some ideas about Americans that might be classified as amateur anthropology of the Captain John Smith variety. But he did perceive that the American tends to fill his day to a degree that appears pathological, compulsive, neurotic, and quite hopeless. He writes: " The American Surgeon does work like hell—and then some. One whom I have visited at length gets up at 5 every morning, goes to bed at 9, and while at work takes no part in social activity." This certainly seems to be a sad existence, and one can only commiserate with this lack of social activity on the part of Ogilvie's anonymous host, whoever he was.

Why does the professor or senior surgeon work so hard at so many different things? Is it a local sign of the national neurosis? Well, it could be so classified, but it also arises from the fact that one cannot conduct an effective teaching surgical service without at the same time conducting a many-faceted organisation that includes personal participation in research, raising funds for men, construction, and research, and lending a hand in various local and national organisations.

Somehow, we feel that your departments—though they may have less money available for research—secure these funds with less " fuss and feathers ", and spend them more efficiently. On the other hand, we are often impressed when visiting large and important surgical departments in the United Kingdom to find that the professor, while a fine clinical surgeon, has little interest in the study of the biological issues of surgical illness, at least as manifested by his own record of research.

The American experience has tended to show that an individual who never has done any research at all (and who therefore has no personal knowledge of the difficulties of trying to ferret out information from Mother Nature by the methods of Claude Bernard) can scarcely be expected to head or conduct a good research programme. He can hire people to do the work, and he may occasionally hire the right person and get some good work done. But, in general, even his own hirelings will find him difficult to deal with when they come with specific requests or with specific plans that he fails to appreciate because of lack of experience—much as the physician fails to appreciate the technical problems of a difficult duodenum merely because he has never dug one out of the pancreas.

With some background experience in research, an individual can foster a reasonably well-balanced research activity in a department, even though he himself can participate in only a small amount of it. It is of egregious importance that he indeed does participate personally with his own two hands, both to maintain his running contact with research, and as an earnest of his own interest and motivation. The day of the " research executive " has happily not yet arrived in surgery. This personal participation in the laboratory adds a facet to the weekly activity of the American surgeon of the university hospital—a facet that is often not viewed and is but little appreciated by the visitor.

Research funds play a very large role in our overall university medical school finance in the United States. The financial support of research constitutes the one major channel by which the tax dollar is ploughed back into private medical enterprise, either in the privately endowed universities or in the State or city universities. One may complain that this represents hidden taxation, or, to the extent that the funds are used for hospital finance, the misspending of money intended for research. But as a practical method of fostering research without fragmenting the national university establishment the National Institutes of Health programme (now in its fifteenth year) has been an unqualified success.

Thus, some of our professorial swarm of activity—" what makes the surgeon run?"—has to do with these things as well as the more familiar aspects of the residency programme, operating, rounds, lectures, and that great institution so well explored on both sides of the Atlantic —The Committee.

A final point that I would like to discuss, having to do with the " American scene ", is the interesting fact that we are sprouting new medical schools at a fairly brisk rate. Since 1930 ten new medical schools have been founded and six schools that have had two-year programmes previously have now developed four-year curricula. Many with part-time clinical teachers are going over to the full-time. This has created a minimum of seventeen new professorial positions in surgery that did not previously exist, and at least a hundred and fifty new top-rank teaching positions in surgery and the surgical specialties.

No young surgeon would expect himself to be considered for a position of responsibility in any one of these new schools if he himself did not know his way around in some field of biological science. He must know both the concepts and the techniques of some advancing field. It is not just a matter of publishing a few papers. He must be a " self-feeder " in terms of investigative ideas. It is not enough to be a good surgeon and a good lecturer. He has also to show himself to be productive. The research fields involved may be as diverse as cerebrospinal-fluid dynamics, renal function, open-heart techniques, hypothermia, or something deeply rooted in the biophysical sciences, such as studies of coagulation, wound healing, calcification, or endocrinology. This allegedly high standard for professorial appointments is satisfactory enough to contemplate in the abstract. But when one comes to the detailed matter of eighty-five medical schools and half a dozen of them opened in the past four years, one suddenly realises that we are getting into a situation where the demand for such people hopelessly outstrips the supply.

Conclusion

Most of the contrasts on two sides of the North Atlantic are minor; but several are of major interest, and all are basic to understanding of surgery in the two countries.

We have unsolved problems in many areas in which you have found very happy solutions, while in other areas we have developed trends peculiar to our own population

and economy, some of which seem quite healthy. There is unquestionably a tremendous opportunity in the United States, both in university surgery and in community practice. Although the frontier officially closed when the last hostile Indian bit the dust, the population growth of the past two decades has created impressive new frontiers of medical need. Many of the contrasts are due to this difference in population-growth rate in the recent past.

REFERENCES

British Medical Journal (1950) ii, 514.
Coller, F. A. (1957) Report to the American Surgical Association.
Moore, F. D. (1959) Metabolic Care of the Surgical Patient. Philadelphia.
Ogilvie, H. (1948) Surgery, Orthodox and Heterodox. Oxford.

LABELLING OF PRESCRIBED MEDICINES

THE following statement has been issued by the Joint Formulary Committee:

There is considerable support for a suggestion that when prescriptions are dispensed, the label of the container should always carry the name of the preparation or drug in order that the contents may be readily identified. It is contended that this would enable a doctor called in to treat the patient of a colleague, when no record of treatment was readily available, to tell at a glance what had been prescribed. It is also claimed that this would provide important safeguards against confusion by the patient where several preparations are concurrently prescribed, and would prevent, for instance, the wrong tablets being taken in error. On the other hand, it has been argued that disclosure of the contents would encourage self-medication with potentially dangerous preparations; for the patient may not appreciate that on another occasion the same symptoms are not necessarily due to the same cause and that a surplus of medicine previously prescribed may neither be any longer active nor suitable treatment. Furthermore, containers are fragile and patients have been known to keep several kinds of tablet in one box.

The Joint Formulary Committee, representing the medical and pharmaceutical professions, has considered this proposal very carefully. It is the duty of the pharmacist to carry out faithfully the exact instructions regarding labelling which are written by the prescriber. It is clearly the duty of the prescriber to decide whether it is in the best interests of his patient that the name of the drug or preparation should appear on the label of the container. The Joint Formulary Committee believes that prescribers are already aware of the advantages of readily identifying the nature of medicines that are prescribed, and wishes to take this opportunity of reminding prescribers that this can be done quite easily.

If it is the wish of the prescriber that the identity of the preparation should appear on the label, he should include with the directions for use on the prescription the desired name or description of the drug. For example:

Label (Sig.) { Phenobarbitone Tablets (strength if required) One to be taken twice daily.

or

Label { Sedative Tablets One to be taken twice daily.

In the absence of these specific instructions the conventional label would read

The Tablets
One to be taken twice daily.

Public Health

LEAD POISONING FROM HOME-MADE WINE

T. P. WHITEHEAD, F.R.I.C. A. P. PRIOR, M.B. Sydney

From South Warwickshire Hospital Group Laboratory, Warwick

DURING this century, lead poisoning has become a rare disease. Occasionally, however, cases do occur as a result of ingestion of lead from bizarre sources. These have included lead nipple-shields, toys, paint, crayons, batteries burned on domestic fires, and even the lead in the print of newspaper used as toilet paper.

Our case of severe lead poisoning was the result of drinking home-made wine.

Case-report

A village butcher, aged 52, was admitted to hospital in November, 1958, on account of abdominal pain of three weeks' duration. The pain was a dull ache in the epigastrium and, although worse on some days, it could not be described as abdominal colic; it was unrelated to food and unrelieved by alkalis. The liver was palpable two fingerbreadths below the right costal margin. Radiological examination of the alimentary canal was normal.

Hæmatological investigation showed a sedimentation-rate of 65 mm. in the first hour (Westergren), and a hæmoglobin of 8·1 g. per 100 ml. The red cells were well hæmoglobinised, and showed polychromasia and basophilic stippling. A tentative diagnosis of lead poisoning was made, and urinary lead determination on two consecutive days showed increased excretion, 0·31 and 0·40 mg. per day. Normally urinary lead excretion is below 0·2 mg. per day.

Questioning the patient about his work, hobbies, and diet revealed no obvious source of lead, but he admitted he was an enthusiastic maker and drinker of home-made wine. He had been doing this for twenty years and had remained well until the past few weeks. He argued strongly that there was no possibility of lead contamination of his wine, and his friends drank as much of it as he did.

The patient asked to be discharged over the Christmas period and we took the opportunity of having various items of diet investigated, including the well water at his home and the beer at his pub, all with negative results. A public health inspector had a look at his wine-making equipment, but there did not appear to be anything unusual in the process, nor was there any obvious source of lead.

Early in January, the patient had an epileptic fit, was readmitted to hospital, and promptly had another. An electroencephalogram showed intermittent bursts of irregular spike activity in both hemispheres. Investigation showed that the anæmia and basophilic stippling of the red cells were still present. Urinary lead determination showed excretion of 0·75 mg. and 1·0 mg. on two consecutive days. Coproporphyrins were present on qualitative examination. We now felt certain of the diagnosis of lead poisoning and the patient

URINARY EXCRETION OF LEAD DURING TREATMENT WITH EDATHAMIL CALCIUM-DISODIUM

Day	Edathamil (g. per day)	Urinary excretion of lead (mg. per day)
1	..	0·75
2	..	1·00
3	3	9
4	3	17
5	3	9
6	3	9
7–9	..	..
10	3	7
11	3	11
12	3	9
13	3	..
21	..	0·46
22	..	0·38

was treated with edathamil calcium-disodium (calcium disodium versenate). This was given intravenously (3 g. per day) in two periods of four days with a three-day break between them. The table shows the resultant urinary excretion of lead. This reached a peak of 17 mg. per day on the second day, and the average excretion during the first four days of treatment was 11 mg. per day. Average excretion of urinary lead during the second four-day period was 9 mg. per day.

With renewed enthusiasm we attempted to show the source of lead. A sample of the patient's home-made elderberry wine was obtained. This was of a rich, red colour and had a not unpleasing bouquet. It had a slightly metallic after-taste, which was scarcely surprising as it contained 7·5 mg. of lead per litre. Without doubt it was the vehicle of administration.

The wine was made by soaking ripe elderberries in a muslin bag in an earthenware vessel, known as a jowl (fig. 1). After forty-eight hours, the liquor was tipped into an electric wash-

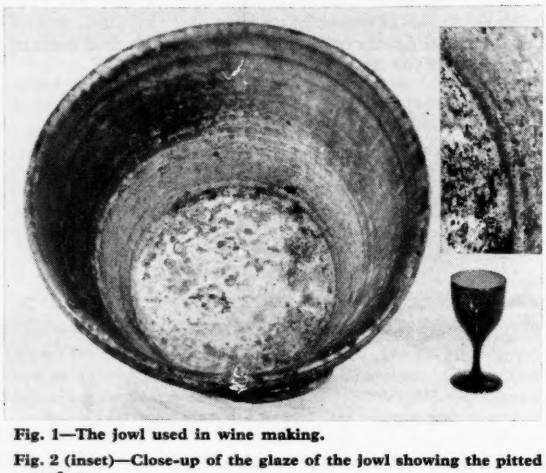


Fig. 1—The jowl used in wine making.

Fig. 2 (inset)—Close-up of the glaze of the jowl showing the pitted surface.

boiler. Here sugar was added and the liquor boiled before being transferred back into the jowl. Yeast was added and the liquid allowed to ferment. When this had reached a satisfactory stage, the liquor was decanted into two earthenware barrels in which it was stored.

To ascertain the source of lead, a litre of hot 1% hydrochloric acid was put into each of the containers used in the process, and the lead content of the resultant solutions was found to be:

Vessel	*Lead content (mg. per litre)*
Boiler	8
Jowl	1000
Earthenware storage-jar (A)	9
" " (B)	7

The earthenware jowl yielded 1000 mg. of lead, and was thus the source of the lead in the wine. With the aid of the British Ceramic Research Association, we ascertained that the jowl was over a hundred years old and was a relic of the age when such containers were glazed with soft lead glazes. The glaze was cracked and pitted (fig. 2) by the acidity of the wine, and pieces of the glaze were even finding their way into the wineglass.

Our patient did, in fact, consume about two pints of the wine a week. The presence of discrete particles of glaze would make it difficult to know precisely the amount of lead consumed before clinical symptoms appeared. He had used this container for the first time in 1958, and had inherited it from an aunt. The container had a local reputation for the flavour and potency of the wine produced in it.

The patient is now well and has a normal urinary lead excretion; his hæmoglobin level and red-cell appearances are normal.

Discussion

Fermented liquors as a source of lead in lead poisoning have a long history. In 1772, Sir George Baker showed that Devonshire colic was due to lead contamination from lead-lined cider presses—and was then denounced from the pulpit as a faithless son of Devon.

During the 19th century in Austria, it was the custom in many country places to put a piece of lead into the wine barrels because the superfluous acid was supposed to be absorbed by the metal and the wine thus improved. This resulted in saleable wine but in many cases of lead poisoning.

Lead contamination of cider from the lead glaze of earthenware storage-jars was mentioned in 1909 (*Lancet* 1909) as a possible explanation of lead poisoning in Dorset.

Masters (1919) investigated earthenware containers used for culinary purposes and showed that, when they were used for storing or cooking food containing malic or citric acids, these plumbosolvent acids could lead to serious contamination of the foodstuffs with lead.

The soft lead glazing of earthenware vessels was a very hazardous process for the pottery workers concerned, and, after the Lancet Commission on Some Leadless Glazes (1899), leadless glazes were adopted and cases of lead poisoning decreased considerably. The Commission was formed to protect workers in the pottery industry. Its valuable work not only saved many lives, but also probably much illness.

It has been stated that there are more than half a million people in this country who brew home-made wines. We were informed that more than three hundred gallons were stored in the various houses in the village in which our patient lived. We have determined the lead content of a number of different samples of home-made wine made and stored in earthenware jars and have found them free from lead.

Lead-glazed containers are probably still used by some home brewers, but the lead contamination is not appreciable until the glaze becomes cracked and broken.

Books which give hints on the preparation of wine in the home have been known to suggest junk-shops as a source of suitable equipment. But antique earthenware should be avoided, and containers with cracked and pitted glazes should be discarded.

Summary

A case of severe lead poisoning is described. The patient was successfully treated with edathamil calcium-disodium (calcium disodium versenate). The source of lead was the glaze of an earthenware container used in making wine in his home.

Our thanks are due to Dr. Stephen Whittaker under whose care the patient was admitted.

We are grateful to the Director and staff of the British Ceramic Research Association for help in the investigation of the glazes of the earthenware vessels used by the patient.

REFERENCES

Baker, G. (1772) *Med. Trans. Coll. Phycns*, **1**, 175.
Commission on Some Leadless Glazes (1899) *Lancet*, **i**, 49.
Lancet (1909) **i**, 665.
Masters, H. (1919) *Lancet*, **i**, 1002.

In England Now

A Running Commentary by Peripatetic Correspondents

Now that we are reconsidering the details of our medical course we feel that we should take every opportunity of giving our students a wide knowledge of the interrelationships of medicine and modern society. A conducted tour of the local brewery is an accepted feature of the class in microbiology in many medical schools, but here we can go one better, for we are on excellent terms, not only with the local brewery, but also with one of the local vignerons, and our enthusiastic microbiologist has already inserted tours of both establishments into the syllabus. On each the exposition is followed by a judicious sampling of the products in rooms thoughtfully provided for the purpose. Only by field-work of this kind, it is felt, will the students acquire a proper respect for the name of Pasteur and an understanding of the basic importance of microbiology. Not only this, but our socially conscious professor of medicine considers it vital that the students should gain some insight into the problems of alcoholism, and feels that this might best be provided by a second visit to the vineyards—a visit on which the conversation would take a very different turn, though the final sampling procedure would be almost identical.

Now the surgeons, in their bluff way, would like to take their tutorial classes along for a historical chat on the use of wine as a surgical antiseptic, and even our pathologist thinks he would find it convenient to expound upon cirrhosis surrounded by a supply of the causative agent. In such an atmosphere we have been forced to meditate on the possibility of making use of these unrivalled facilities for the benefit of preclinical students. It has been urged, for example, that our lectures on the mechanisms of swallowing might be supplemented by practical work in the field, or that a class on reaction-times could be profitably arranged. We ourselves see no need to advance such specious arguments, for we well remember an educational experience we had some years ago, when the medical society of which we were then a member invited a director of a wine firm to guide us through a small selection of his wares.

The wines were ranged in line on a white-covered table, with reinforcements underneath. The society gazed solemnly through the glasses at the guttering candles provided, it inhaled the aroma up the backs of its noses, and for the first three bottles or thereabouts it spat out the mouthfuls into a bucket in professional style. But when it came to one it liked, the discipline broke down, and by the time it reached the sixth or seventh bottle it was drinking heartily. Afterwards we were surprised to find that our ranking of the first four was identical with that of the society's impresario, though our vocabulary was not in his class. For example, what we had said about the Châteauneuf-du-Pape 1947 was "alpha minus; taste good, colour good, smell good". What we should have said was "A noticeable burnt, roasted flavour; a very good glass of wine". Of the winner, a Corton 1928, our notes read: "alpha; very pleasant". This, we found, was "A beautiful glass of wine, lacking the astringent pull of young wine. Lovely smooth soft drinking, with a wonderful breeding and bouquet. The finest drink on the slab". Of the Fleurie 1950, which was last in order of sampling, we had written, in handwriting by this time grown rather large and expansive: "Undistinguished". Clearly we had begun to find our form, but what we had really meant was: "A hard, unyielding, unforthcoming wine, a little harsh on the nose".

It seems obvious to us that an organised wine-tasting is in itself an excellent educative procedure to include in the preclinical curriculum. It would develop all those qualities which the clinicians find deficient in our students—their command of language, their powers of observation and description, and their capacity to synthesise information and come to a decision. We are bringing the matter to the notice of the Faculty tomorrow.

* * *

Medicine, I was taught, is an art and an inexact science. However, I like to try to keep up with the scientific advances, and when a colleague told me he had just acquired a new American instrument which could be used for every conceivable sight-test I was delighted to accept his offer to show it to me. My friend explained that the machine had only just arrived and he was not sure how it worked, but his technician knew how to use it and would explain it to me. The explanation was somewhat involved, so I suggested he should test my eyesight so that I could follow a practical demonstration. After fifteen minutes the machine produced a series of figures which were then decoded. The result was startling. It appeared that I needed a bifocal monocle, and for good measure the instrument had added that I was unsuitable for employment as an airframe-fitter or a fettler.

* * *

During that grim time between the end of breakfast and departure for work, one of the twins was polishing her nine-times table and making heavy weather of it. While helping her I made the following discovery.

If you multiply an even number by an even number the result is always an even number. If you multiply an odd number by an even number the result is likewise an even number, and if you multiply an even number by an odd number, once more, an even number results.

Only if an odd number is mated with an odd number is the product of conception an odd number. Stated simply:

$$E \times E = E$$
$$E \times O = E$$
$$O \times E = E$$
$$O \times O = O$$

Obviously this is simple Mendelian genetics. "Evens are dominant, and odds are recessive," and one can predict that in any large series of numbers—say 1 to 100—the ratio of even numbers to odd must be 3 : 1. But I am assured this isn't so; they occur in equal quantities in a system known as recurrent bimodal distribution.

Now, obviously, if Mendelism doesn't work in the realm of pure mathematics it won't work for sweet peas, or blood-pressure, or piebald and skewbald horses, or anything else in biology. I'm terribly sorry, but I'm afraid I've upset the whole basis of modern genetics. Perhaps, however, it will now be possible to reconcile Professors Platt and Pickering since the whole business of genetics is clearly nonsense.

Of course, some smart Alec will say "he's forgotten the prime numbers". Since prime numbers are, by definition, odd numbers we must remove them from our series from 1 to 100 first. I've done this and the ratio is still not what it ought to be —1 : 3. Try it and see.

* * *

Recent advances in the study of chromosomes must not blind us to the fact that a great deal of much more fundamental work must have been done on the quiet in America. An embryologically minded colleague, back from the United States, informs us that in a clothing store he observed a cupboard labelled on one side "Boys' Genes", and on the other "Girls' Genes".

* * *

News from School.—"We had a total defeat against M—, not because we were worse but because we had so many serious injuries. There were six complete write-offs during the match. Capt. Rugger knocked unconscious, recovered in our sanatorium (match was away —about 2 hours distant). Secretary Rugger dislocated right arm. 'M' wing three-quarter fractured thigh and is in hospital. Somebody, a forward kicked between the legs and carried off unconscious. Scrum half got a 4 in. cut on knee, had to be stitched. Two opposing 'blocks' carried off. One was unconscious with a fractured skull. The other went off unconscious from a kick in the solar plexus and is now in hospital critically ill with kidney trouble (ruptured kidney I think). So it was a pretty rigorous game. They won 18-3.

"I went to a film on the Royal Ballet. We saw extracts from *Swan Lake* and *Firebird*. It wasn't bad but I wouldn't go again."

Letters to the Editor

REFRIGERATED VENTILATION FOR OPERATING-THEATRES

SIR,—Your editorial review (Dec. 3) of the outstanding new book on *Hospital Infection* by Williams, Blowers, Garrod, and Shooter [1] wisely challenges certain points of view in this otherwise admirable work. I should like to reinforce your remarks about the need for refrigerated ventilation plant in operating-theatres. To say, as the authors do, that " in London, the daytime maximum temperature exceeds 77°F on an average of only twelve days of each year " is surely to *justify* and not to disprove the need for refrigeration plant.

Perhaps I may be permitted to illustrate this subject by reference to a newly completed theatre suite at St. Albans Hospital. There we have had the valuable advice and collaboration of Dr. Blowers himself on certain aspects of the ventilation system. From the strictly bacteriological point of view it may be said that the system is excellent. But, from the point of view of atmospheric conditions in the theatres during hot weather, our plant is both inadequate and dangerous. I hasten to add that Dr. Blowers is in no way responsible for the faulty basic design imposed on us by the Ministry of Health.

The past summer has been notable for its poor weather and generally low temperatures, and our experience with this unrefrigerated ventilating-plant is consequently all the more significant. On May 17, 1960, at 2 P.M. the atmospheric conditions outside the theatre suite were temperature 63°F and relative humidity 53%; within the theatres, 76°F and 82%. On May 31 the morning conditions within the theatres were 75°F and 77%. On June 5 the temperature in the theatres was 82°F (humidity not recorded because no wet-bulb thermometer was available). On June 17 (a rather " sticky " day) the outside temperature was 78°F and relative humidity 82% at 11 A.M.; within the next six hours the temperature inside the theatres rose from 75°F to 86°F, and humidity from 90% to 95%. These admittedly selected samples from our records bear witness to the intolerable conditions which can be created by inadequate ventilation equipment of this type even during a bad summer.

The most important reason for giving publicity to this subject is to ensure that unrefrigerated ventilation plant is not installed in other theatre suites. Before the installation of the St. Albans plant, and acting on the advice of an independent consulting ventilation engineer, our surgical staff clearly warned the regional hospital board and the Ministry of Health of the inevitable consequences of their action. Despite that warning and repeated requests that the plant should be modified no effective action has been taken. If the Ministry of Health is waiting for more convincing factual evidence in the form of a corpse of a patient dead from heatstroke, then it seems possible that we may have to wait until next summer to provide it. In the meantime it is surely a pity that an excellent book by four such eminent bacteriologists should seem to lend authority to the wrong and thoroughly misguided views enunciated in the Ministry of Health Bulletin on operating-theatres.[2]

London, W.1. REGINALD S. MURLEY.

1. Williams, R. E. O., Blowers, R., Garrod, L. P., Shooter, R. A. Hospital Infection: Causes and Prevention. London, 1960.
2. Hospital Building Bulletin no. 1: Operating Theatre Suites. H.M. Stationery Office, 1957.

ADMINISTRATION IN MENTAL HOSPITALS

SIR,—Dr. Bardon (Nov. 12) is bluffing when he implies that the tremendous opportunities for advance offered to mental hospitals by the Mental Health Act are lost by refusal to accept (his) basic principles of hospital administration.

In the first place, the Mental Health Act does not offer such opportunities, and, in the second place, medical superintendents at such hospitals as Dingleton, Netherne, Mapperley, and Warlingham Park made tremendous advances before the new Act without Dr. Bardon's recommendations.

Indeed, having served with Dr. Bardon on a medical advisory committee, I think he would be the first to agree with me that it was not his experience that the medical advisory committee was capable of agreeing on a common policy which they could implement. In fact it was the disagreement and perpetual stalemate that resulted in junior doctors innovating some of the advances that were made.

Furthermore, at that hospital all consultant psychiatrists had complete clinical control of their beds without interference from the medical superintendent, but did not themselves initiate any tremendous advances.

For these reasons I am puzzled that Dr. Bardon should recommend so strongly a system which his experience and the available evidence has shown to be inadequate, thus depriving psychiatric hospitals of positive leadership so urgently needed during the next few years.

I wonder if any medical advisory committee would have had the foresight and knowledge to produce policies such as open doors, unrestricted visiting, and all the other advances which have been made to control institutional neurosis in the past decade.

Theoretically a group of consultant psychiatrists and senior hospital medical officers mature in outlook, unbiased in judgment, widely read, and in touch with modern trends would be able to produce ideal working policies and implement them. Many who know, if they are really honest with themselves, what actually happens at medical advisory committee meetings would have to doubt if the petty and often personal squabbling that goes on would ever enable a policy to be produced, let alone implemented.

Senior administrative medical officers are acknowledged to be necessary to regional boards. A psychiatrist in charge of a department is thought to be necessary in a teaching hospital, and a chief medical officer is realised to be necessary at the Ministry of Health. It may be such systems of medical administration are mistaken, but I doubt it.

In psychiatric hospitals the situation is different. It is time somebody stated publicly (I had hoped somebody else would do so) how incompetent many consultants and S.H.M.O.s in psychiatry are, both in their work and in affairs generally. I do not think it would be fair to patients or to junior doctors in psychiatric hospitals to inflict one of these people as their director in the interests of democracy. It is not, I suspect, by chance or victimisation that merit awards in psychiatry are so much rarer than in other specialties. Nor is the attitude of physicians and surgeons to psychiatrists entirely due to the prejudice or the state of psychiatry as a science.

It may be that the medical director, superintendent (call him what you will), should be elected by consultants, consultants should be elected by junior hospital staff, and perhaps qualification should be democratically bestowed by students on their fellows—it is doubtful. As I see it, selection of the more industrious and capable psychiatrists for the role of chief-of-service or consultants by a panel of experts is a more satisfactory solution. Similarly in the case of matrons.

No-one can deny that the position of medical superintendent has been abused and misused in the past, but, then, so has the

position of consultant psychiatrist. I have known junior doctors who bitterly resent doing most of the work in a mental hospital under the pretext of "being trained", while a consultant did very little and received four times the pay, together with miscellaneous privileges and status.

To me it seems contrary to the spirit of medicine that either a medical superintendent or consultant should continue indefinitely in office, regardless of his performance, professional competence, and industry. Practical solution is not easy but not impossible. Everyone cannot but agree that a system which prevents patients benefiting from the more competent administrations of some doctors in order that an incapable official is well paid is highly undesirable.

There can be no doubt that every psychiatrist should be free to do what he ought to do but not necessarily free to do what he likes. Until the evolution of some method of getting rid of those who are concerned with their rights but neglect their obligations, I submit it will be foolish of the Ministry or medical profession to be rattled any further by the disgruntled vociferous group who confuse the shortcomings of the personality of some medical superintendents with the system of administration of which they are part. A careful investigation into the contribution made to psychiatry by these individuals with a "thing" about authority would prove very interesting.

Severalls Hospital,
Colchester,
Essex.

RUSSELL BARTON.

SIR,—Dr. Kidd's letter of Dec. 3 marks a considerable advance on this subject. However, a point which I think has been insufficiently emphasised is the importance of medical staff committees as described in the Ministry of Health circular H.M.C. (53) 87. In many mental hospitals these committees have scarcely begun to function adequately. The old idea that the medical superintendent alone need be consulted lingers on, and the rest of the senior medical staff have no contact with the management committee.

The posts of chairman and secretary to the medical staff committee should rotate among the senior medical staff at least once every three years. Both these officers should have direct access to the chairman of the management committee at least once a month. Without some such procedure, it is not practicable for the medical staff to make their views known or be aware of hospital policy.

Littlemore Hospital,
Littlemore,
Oxford.

J. E. DUFFIELD.

SIR,—I am prepared to agree with Dr. Kidd that evolution is preferable to revolution but would suggest that there is nothing very revolutionary about asking that the relationship between management committees and medical staff in mental hospitals should be one of mutual respect and courtesy. I agree that the Mental Health Act has nothing to say about how a hospital is administered, nor did I say that it has. I did say that the Act offers mental hospitals tremendous opportunities to advance, and I suggest that one of the opportunities it offers is the evolution of the relationship between hospital management committees and medical staff mentioned above. Dr. Kidd (Oct. 29) clearly indicated that he believes that the presence of a medical superintendent in the administrative structure hinders this evolution by causing the hospital management committee ". . . to take more notice of his monthly reports than the resolutions of the medical advisory committee".

I will leave it to matrons, chief male nurses, and others to comment on Dr. Kidd's suggestion that it is part of the function of a medical superintendent ". . . to interfere in matters of administration and discipline of medical and nursing staff", and that he should be answerable for such interference, not to his medical and nursing colleagues, but to hospital management committees or regional hospital boards.

With regards to Dr. Kidd's suspicion ". . . that powerful unconscious motives may be at work" in determining the point of view of many clinical psychiatrists, I presume he would agree that the imputation or even the demonstration of motive behind a proposition does not make the proposition false.

Shenley Hospital,
near St. Albans,
Herts.

D. BARDON.

DEFERRED MITRAL VALVOTOMY: A CONTROLLED SURGICAL TRIAL

SIR,—Your annotation [1] reviewing retrospective studies of groups of patients with well-developed mitral stenosis, treated medically and surgically, leaves little doubt which is the correct treatment once a critical stage has been reached but, as you suggest, "it is doubtful whether the patient without symptoms or systemic embolism should be subjected to the operation as a prophylactic measure".

In an endeavour to remove this doubt, a controlled trial of early surgery versus conservative medical treatment in patients with established stenosis but few symptoms other than moderate breathlessness on exertion was started in Cardiff in 1955. The trial was never completed because fewer local cases were available than had been expected, and the climate of medical opinion moved away from early surgery whilst it was under way. Our experience is none the less relevant to current discussion of the problem.

In 1955 the ethical difficulty of allocation into two groups, for early surgery on the one hand or medical treatment and possibly deferred surgery on the other, was simplified for us by the existence of a waiting-list of patients; random allocation could therefore ethically be used to decide whether the patient would be recommended for immediate operation or deferred for a period under close medical supervision. In our experience medical criteria of suitability for inclusion in the trial can be fairly easily defined; the definition of surgical criteria is more difficult because the surgeons' willingness to operate also depends on the patients' attitude and willingness to undergo operation. In the Cardiff trial, cases were included on a random basis only after this consent had been freely given by patients considered potentially suitable for valvotomy in other respects.

Early operations were performed within two months. At six-month and twelve-month intervals all subjects were followed clinically and physiologically, the principal aim of the latter being to provide objective evidence of exercise tolerance and cardiopulmonary function during exercise. In the course of eighteen months, 23 apparently suitable cases in the age range 20–44 years were seen and referred, each to two medical referees. Of these, 9 were accepted for inclusion in the trial; 5 for early operation and 4 in the deferred operation group. During the succeeding four years, 1 of the deferred cases has come to operation and another has been excluded on account of anæmia. 1 of the cases operated on, a man aged 34, has had a recurrence of rheumatic fever.

The trial has been abandoned for the reasons mentioned, but we are of the opinion that this approach is still needed to discover the best method of treatment for those with few symptoms but definite signs. In view of Dr. Bannister's findings [2] it might now be considered reason-

1. *Lancet*, Oct. 1, 1960, p. 748.
2. Bannister, R. G. *ibid.* Aug. 13, 1960, p. 329.

able to limit it, at least in the first instance, to those under the age of 40. But it is, one hopes, in this group that most of the new cases will be detected over the coming years.

It is our impression that there is still considerable divergence of view between different centres on the correct treatment for early mitral stenosis, and as a result there is in effect an uncontrolled trial in progress in the country as a whole. It seems a pity that this divergence of view and uncertainty cannot be used to carry the knowledge of the correct treatment of mitral stenosis a stage nearer perfection.

J. E. COTES, BYRON EVANS, H. M. FOREMAN, J. C. GILSON, H. R. S. HARLEY, P. D. OLDHAM, WILLIAM PHILLIPS, HAROLD SCARBOROUGH, DILLWYN THOMAS, A. J. THOMAS, L. R. WEST.

M.R.C. Pneumoconiosis Research Unit, Cardiff United Hospitals, and Sully Hospital, Glamorgan.

SURGERY OF PAINFUL HIP

SIR,—During the past two years I have seen fifty cases of painful hip. In most of these, shortening of the gracilis muscle limited abduction, and caused a little flexion of the hip and (on lying flat on the back) of the knee. Most of these patients had been advised to have the hip replaced by a metal or plastic joint, or to have the hip-joint immobilised by pinning. Instead, I have divided the gracilis tendon near the pubes, and in all these cases this has stopped the pain and greatly increased the mobility.

The operations were carried out under local anæsthesia. The gracilis muscle is readily recognised because it has a shining tendinous sheath at its origin. (It is the only muscle in this region with such a sheath, and I wonder whether this tendinous sheath has anything to do with its shortening.) Before the tendon is divided, it should be injected with a local anæsthetic, because it is very tender. There are often fibres through the muscle, and these must be divided. In some cases the muscle should be cut right through: indeed I rather think that this is best in the majority. A drainage tube should always be inserted, and personally I always use 1/8000 perchloride of mercury throughout the operation, to prevent sepsis.

These patients did not have rheumatoid arthritis in the hands, wrists, elbows, or ankles, and I do not think that the painful hip was due to this condition. I operated on two cases of painful hip with rheumatoid arthritis in the wrists, hands, and elbows, and, though the pain was not entirely relieved, mobility was increased.

Sandhurst, Kent. V. NESFIELD.

MAGNESIUM SULPHATE IN THE TREATMENT OF CORONARY THROMBOSIS

SIR,—There is need in general practice for an alternative to anticoagulant therapy. Though its efficacy is well attested it has considerable drawbacks, quite apart from the nuisance of repeated blood-tests.

Phenindione therapy, for example, is not without complications, such as hepatitis,[1] drug fever, and neutropenia,[2] and may have to be stopped because of unexpected hæmorrhage. It is unsuitable for patients with impaired liver function, peptic ulcer, &c. Even a dormant pile may be a contraindication, as in one of my early patients who became severely anæmic from this cause.

Within the past year another patient (with an apparently safe prothrombin level on the day of onset) had severe hæmaturia which persisted for two days despite repeated intravenous injections of vitamin K_1, another developed intractable epistaxis requiring blood-transfusion, and a third was unsuitable because the infarct complicated an operation for jaundice due to common-bile-duct obstruction. This experience may be unfortunate but I doubt if it is rare.

Even when therapy could be safely continued in hospital it had to be stopped on discharge because the patients were scattered over wide areas beyond laboratory control. For all these reasons I now resort to treatment with parenteral magnesium sulphate. This was first described in 1956 by Malkiel-Shapiro and his coworkers [3] in South Africa, with very favourable results, and similar results were obtained in Tasmania last year by Parsons et al.,[4] who wrote: "Over 100 patients suffering from coronary heart disease (of which at least one third were acute myocardial infarctions) were treated with intramuscular magnesium sulphate with only one death, while 196 cases of acute myocardial infarction treated with routine anticoagulants gave a 30% mortality."

Magnesium salts are known to protect rats against experimentally produced myocardial necroses [5] and endomyocardial fibrosis,[6] which provides a basis for the belief that they may be beneficial in man. It has been shown, too, that a correlation exists between serum-magnesium and serum-cholesterol levels in man,[7] which may have a bearing on coronary atherogenesis.

The simplicity of the treatment makes it eminently suitable for general practice especially in countries like this, and its apparent safety and effectiveness justify further trials. The 6 cases I have treated recently are too few for valid conclusions, and I should be grateful to know the results of any further large trials or whether any are contemplated.

Nakuru, Kenya. A. L. CRADDOCK.

ORAL TREATMENT OF PERNICIOUS ANÆMIA WITH LOW DOSES OF H.P.P./1

SIR,—Dr. Smith (Nov. 19) is not strictly accurate when he refers to the correspondence between Dr. Varadi and ourselves as an "argument", for we have expressed no opinion, as yet, on the significance of serum-B_{12} levels on H.P.P./1 therapy.

We have merely attempted to discover from Dr. Varadi what scientific evidence he has for his conclusion that the serum level reflects the degree of intestinal absorption, on this form of therapy. Judging from his letter of Nov. 19, his conclusion seems to be based on an experiment yet to be performed.

Dr. Shinton too (Nov. 5) speaks of the rational concept of restoring the serum-B_{12} level to normal, but unless the serum/tissue relationship is known on this form of therapy, his statement is no more than a half-truth, and could, therefore, be misleading. Theoretically, one of three things could happen to a hæmopoietic agent after absorption from the gut—excluding loss from excretion. Firstly, it might be selectively absorbed from the serum by the tissues, thus giving a higher tissue than serum level of vitamin B_{12}. Secondly, the absorbed agent might become largely bound to the protein of the serum, thus giving a disproportionately high blood level as compared with that in the tissues. Thirdly, the hæmopoietic agent might be distributed equally after absorption, between serum and tissue.

In our opinion, until one knows which of the three possibilities actually occurs on H.P.P./1 therapy, there is no point whatsoever in attempting to draw any conclusions from the serum-vitamin-B_{12} concentrations alone. The danger in so doing is a serious risk of discrediting a highly acceptable hæmopoietic agent merely because the first of the three possibilities has occurred. Conversely, a relatively inactive preparation might yield disproportionately high serum-B_{12} levels because of binding to the serum-proteins.

We agree, substantially, with the rest of what Dr. Smith says in his letter. Certainly we think that, having established the clinical superiority of H.P.P./1 over oral crystalline B_{12}, the

1. Jones, N. L. *Brit. med. J.* Aug. 13, 1960, p. 504.
2. Mather, G., Riley, C. *ibid.* p. 506.
3. Malkiel-Shapiro, B., Bersohn, I., Terner, P. *Med. Proc.* 1956, ii, 455.
4. Parsons, R. S., Butler, T., Sellars, E. P. *ibid.* 1959, ii, 487.
5. Selye, H. *Brit. med. J.* 1958, i, 599.
6. Selye, H. *Lancet*, 1958, i, 1351.
7. Bersohn, I., Oelofse, P. J. *ibid.* 1957, i, 1020.

important thing now is to discover whether the treatment remains successful over a period of years. We do not, however, share Dr. Smith's belief that oral therapy will never supersede the parenteral treatment of pernicious anæmia, and we doubt whether his enthusiasm for securing vitamin B_{12} in two or three inches of muscle would be shared by most of his patients.

St. Helens Hospital, St. Helens, Lancs.

F. S. MOONEY
J. G. HEATHCOTE.

"THEY NEVER TELL YOU ANYTHING . . ."

SIR,—Even if there are difficulties with doctor-patient communication, need there be any with that of doctor-relative?

My mother was a hospital patient and up to her discharge the most I could ascertain was that she had undergone a major operation. The knowledge that I am a hospital administrator failed to loosen the shackles of silence. I never saw the medical staff when I visited, which owing to distance was not very frequently, but surely the ward-sister is sufficiently responsible to impart some kind of information. The fact that my mother is over 80 made the situation more absurd, or so it seemed to me.

Wembley.

P. E. WINDO.

PULMONARY EMPHYSEMA

SIR,—Dr. Rappaport and Dr. Mayer (Dec. 3) have written a provocative article. Some of their assertions demand close scrutiny because questions are raised which they do not attempt to answer.

Early in their paper they dismiss the lung as "primarily an organ of motion". How else can one visualise it? Do they really believe that ventilation plays so small a part in the normal and disordered physiology of the lung?

"Chronic bronchiolitis and bronchitis of insidious origins" are not, according to Dr. Rappaport and Dr. Mayer, significant in the pathogenesis of emphysema. Yet later in the paper they list as possible causes "the whole gamut of infections—allergic inflammations, and toxic (physical or chemical) agents which reach these structures either by the blood-stream or by inhalations (fine aerosols)". One fails to see the difference between these processes and that of chronic bronchiolitis and bronchitis.

They also state that emphysema may be initiated by failure of "visceral function . . . non-functioning air spaces enlarged by *coalescence of alveoli* and kept open by thoracic traction become subject to mechanical enlargement by air trapping". The writers do not say by what process coalescence of alveoli takes place. If they deny that these alveolar changes are secondary to bronchiolar dysfunction, what process do they envisage as causing alveolar coalescence with enlargement of the air sacs? In this context I would refer to the work of Krahl.[1] Krahl installed an artificial ball-valve in the bronchus of a rat's lung which offered resistance to expiration and caused local inflammation in the airway. After the valve had been in position for some time, the lungs distal to the valve showed grossly discernible distension of peripheral airways with tendency to collapse. Microscopically there was "*degeneration of the alveolar septa with formation of abnormally large air spaces*". This important paper adds weight to the evidence that emphysema begins primarily as bronchial obstructive disease, and that the alveolar changes are not primary.

Dr. Rappaport and Dr. Mayer are convinced that in some cases of emphysema no acquired disease is present, and in these cases postulate "pre-existing defects in the lungs of post-natal developmental origin". It would be of interest if the authors would explain just what is meant by this.

Seemingly, they ascribe emphysema to a primary loss of visceral lung function, by which they mean loss of diffusion surface for the lung. All the disorders of ventilation, including changes in air flow, residual volume of air, and derangement of the mechanics of breathing, are dismissed as secondary effects following primary coalescence of the alveoli—a process which they totally fail to explain in terms of ætiology.

Bearing in mind the observed clinical facts of the relationship of emphysema to bronchitis, either infective or chemical (smoking, air pollution, cadmium, &c.), and in view of the experimental evidence described above, it is difficult to accept the explanation given in this article. The loss of diffusion capacity may be explained as a *secondary* phenomenon following the loss of available diffusion surface. This loss of diffusion surface is surely due to the breakdown of the alveolar septa, which in turn follows bronchiolar obstruction.

Until Dr. Rappaport and Dr. Mayer provide additional evidence, their argument must surely remain theoretical and unproven.

The London Hospital, London, E.1.

B. H. BASS.

1. Krahl, V. E. *Amer. Rev. resp. Dis.* 1959, **80**, 158.

SHINGLES AND CHICKENPOX

SIR,—Having followed with interest the recent letters about zoster and chickenpox, may I cite a very up-to-date case, which bears out Colonel Foster's letter of Dec. 3.

A young man developed pain at the back of the neck on Nov. 14 and a few macules two days later. After another two days he had typical zoster of C2 and C3. On Nov. 30 his 7-year-old daughter became "off colour" and on Dec. 3 a typical chickenpox rash appeared. There was no known contact of chickenpox, nor do I know of any local cases. This works out as: prodromata zoster to stated prodromata chickenpox 17 days; rash of zoster to rash of chickenpox 17 days.

London, E.2.

G. LAWSON.

PULMONARY HYPERTENSION

SIR,—Would Dr. Goodwin and his colleagues (Oct. 8) explain how they can diagnose "slight right ventricular hypertrophy" clinically—i.e., at the bedside?

Moreover, is it possible to be certain that a second pulmonary sound is "narrowly split" when over the same area an ejection click and a systolic murmur are reputed to have been heard? In other words, the authors claim that with each heart-beat, a period of time which is less than one second, they can hear over a small area five different sounds, accurately identify them, and report on them each individually.

Do many other of your readers claim to have these abilities, which, incidentally, are rivalled by another cardiologist who maintains that he often hears eight different sounds in the mitral area with each heart-beat and can identify accurately and report on each individually? Of course I do meet many postgraduate students who make similar claims but I do not take them seriously as they are very rarely successful in the M.R.C.P. clinical examination, because they fail to diagnose the very elementary heart cases which are shown.

London, W.1.

M. H. PAPPWORTH.

*** We showed this letter to Dr. Goodwin, whose reply follows.—ED.L.

SIR,—Slight right ventricular hypertrophy is diagnosed at the bedside by the presence of a diffuse tapping cardiac impulse felt to the left of the sternum, accompanied by a gentle lift of the sternum. The normal left ventricular thrust may still be felt, but often the left ventricle is impalpable.

Normally the 2nd heart-sound is single on expiration but separates clearly on inspiration into its two components of aortic and pulmonary valve closure. Narrow splitting indicates that this normal separation on inspiration is reduced in degree, and on quiet breathing the two components of the sound are closer to each other than normal. Increased pressure in the pulmonary artery leads to more rapid apposition of the cusps of the pulmonary valve, which causes the sound component of the second heart-sound to occur earlier. Narrow splitting is thus a useful sign of pulmonary hypertension, and is often accompanied by increase in intensity of the pulmonary component.

The ejection click occurs in systole well before the second heart-sound, and the systolic murmur (which is due to ejection of blood under increased pressure through a dilated pulmonary artery) is heard as a longer, lower-pitched sound than the click, which is high-pitched and short.

We feel that experienced auscultators will confirm our ability to detect in the same patient an ejection click, an ejection systolic murmur, and narrow splitting of the second heart-sound.

These physical signs are not mere figments of the imagination, but are vital links in the chain of evidence which leads to the diagnosis of pulmonary hypertension. For the inexperienced, they are not always easy signs to elicit, but their recognition at the bedside is most important, for they contribute to the detection of diseases which may be curable if treated early but which if undetected may prove fatal.

Postgraduate Medical School,
London, W.12. J. F. GOODWIN.

ANTICOAGULANT THERAPY

SIR,—I have been misquoted in your account (Dec. 3, p. 1247) of the symposium on anticoagulant therapy.

In an attempt to estimate the requirement for long-term anticoagulant therapy, I obtained from 30 general practitioners, covering 70,000 of the population, the numbers of their patients (*a*) who had suffered a myocardial infarction within the two previous years and were still alive, and (*b*) who were suffering from angina of effort.

From these figures 1% of the population require long-term anticoagulant therapy *not* 10% as stated in your report.

University Department of Medicine,
Royal Infirmary, Glasgow. A. S. DOUGLAS.

A SUCKER FOR EMPTYING THE INTESTINE

SIR,—Mr. Lawrie's account (Nov. 19) of a sucker for evacuating the small intestine prompts this report of a cheap " home "-made instrument.

It is made from a suitable length of semirigid, medical-grade, thin-walled, polyethylene tubing. Holes as required may be drilled with a dental burr, and the end plugged with polyethylene rod, if considered necessary. During sterilisation a metal or glass rod is placed inside the tube to preserve its straightness till it is cool again.

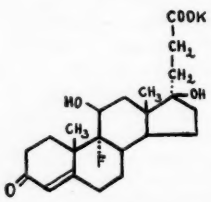
It is connected to the sucker tube by a glass connection (' Viules ' cartridge). It may be extended in length by further pieces of tubing plus an extra glass connection.

If necessary, this simple contraption may be made in several different diameters. Its lightness is a very desirable attribute, and if necessary it can be bent.

Kuala Belait,
State of Brunei,
British Borneo. KEITH F. D. SWEETMAN.

PROTECTION BY ANTI-MINERALOCORTICOID AGAINST AN OTHERWISE FATAL DIHYDROTACHYSTEROL INTOXICATION

SIR,—Spironolactone, an anti-mineralocorticoid, inhibits the otherwise fatal cardiac necroses that are produced in rats by pretreatment with fluorocortisol and subsequent exposure to the stress of restraint.[1] Recently, Mr. E. A. Brown, of G. D. Searle & Co., Chicago, Illinois, synthesised ' SC-11927 ', a much more potent anti-mineralocorticoid that is not a spirolactone but has the formula 3-oxo-9α-fluoro-11β, 17β-dihydroxy-17α-pregn-4-ene-21-carboxylic acid (potassium salt).



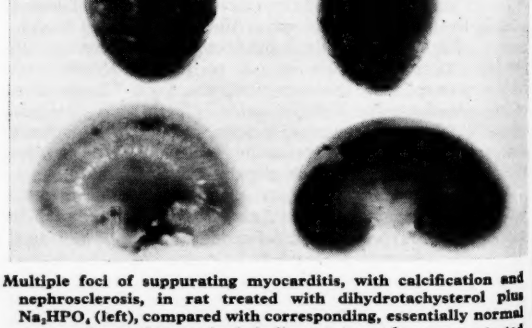
We found that this compound is even more active than spironolactone in blocking the cardiotoxic effect of fluorocortisol plus stress, and the question arose whether it could also inhibit the cardiovascular toxicity of compounds other than corticoids.

50 female Holtzman rats, with a mean initial body-weight of 101 g. (± 0·68 g.), were subdivided into five equal groups and treated as shown in the accompanying table. For the production of cardiovascular damage, the animals of all groups were treated with 35 μg. dihydrotachysterol (' Calcamin ') and 2 mmol. Na_2HPO_4 mixed together and administered by stomach tube, in 2 ml. of water twice daily. SC-11927 was given, at the doses in the table, in 0·2 ml. of water subcutaneously twice daily. The experiment was terminated on the 5th day by killing all survivors with chloroform. Immediately after necropsy, hearts and kidneys were inspected with a binocular loupe, then fixed in neutral formalin for examination of sections stained with hæmatoxylin-phloxine and the v. Kóssa

PROTECTION BY SC-11927 AGAINST CARDIAC AND RENAL LESIONS

Group	Dose of SC-11927 (μg.)	Final body-weight (g.)	Cardiac lesions (scale 0–3)	Nephro-calcinosis (scale 0–3)	Mortality
I	0	96 ± 2·24	2·4 ± 0·27	2·7 ± 0·15	90%
II	5	98 ± 2·30	2·2 ± 0·41	2·7 ± 0·23	60%
III	10	97 ± 2·54	1·8 ± 0·44	1·7 ± 0·37	60%
IV	100	117 ± 1·45	0	0	0
V	500	119 ± 2·90	0	0	0

1. Selye, H. *Proc. Soc. exp. Biol., N.Y.* 1960, **104**, 212.



Multiple foci of suppurating myocarditis, with calcification and nephrosclerosis, in rat treated with dihydrotachysterol plus Na_2HPO_4 (left), compared with corresponding, essentially normal organs of a rat that received similar treatment but was protected by minimal effective dose (100 μg.) of SC-11927.

calcium stain. The readings given in the table are the means (with standard errors) of macroscopically and microscopically observed organ lesions expressed in terms of an arbitrary scale of 0 (no lesion), 1 (slightest detectable lesion), 2 (moderate lesion), and 3 (most severe lesion).

All but 1 of the controls died, exhibiting even macroscopically evident lesions of suppurating myocarditis, with calcification of cardiac muscle and coronary arteries as well as pronounced nephrocalcinosis, as previously described.[2] SC-11927 proved to be virtually ineffective in doses of 5 and 10 μg. Rats treated with 100 or 500 μg., however, were completely protected as regards loss of body-weight, cardiac lesions, nephrocalcinosis, and mortality.

Two possible explanations of this protection should be considered:

(1) Although SC-11927 is a potent anti-mineralocorticoid, it may have blocking actions against compounds other than corticoids, such as dihydrotachysterol.

(2) The fatal cardiotoxic and nephrotoxic actions of dihydrotachysterol plus Na_2HPO_4 may depend upon the "conditioning" action of endogenous mineralocorticoids; if so, blockade of the latter would abolish the toxicity of the treatment administered.

SC-11927 exhibits no detectable inherent toxicity per se when administered at ten times the prophylactic dose level, and even sudden intravenous injection of 2·5 mg. of this compound produces no demonstrable damage. Hence, further studies concerning the possible prophylactic actions of this anti-mineralocorticoid against lesions not primarily due to mineralocorticoid intoxication seems to hold promise.*

This work was supported by grant No. H-3688(C3) from the National Heart Institute, U.S. Public Health Service, and by a grant from the Gustavus and Louise Pfeiffer Research Foundation.

H. SELYE
S. GRASSO
N. PADMANABHAN.

Institut de Médecine et de Chirurgie expérimentales, Université de Montréal, Montreal.

RETIREMENT OF MEDICAL RESEARCH-WORKERS

SIR,—Nowadays medical research-workers usually retire at the age of 65. With a life of scientific discipline behind them, many could do useful work for some further years. A few are snapped up by pharmaceutical firms with which they have had previous contact; a few go to W.H.O. or to staff embryo Commonwealth medical schools, or are allowed a corner in a University laboratory; a group of elite who would otherwise have retired are producing first-class research in an institute near Cambridge. These facts indicate sustained competence. A large number, from inclination or for health reasons, probably wish genuinely to disengage. A significant number, however, would like to work but are too diffident to mention this audibly: influenced by old-age inferiority feelings, obsessed by forgetfulness of colleagues' names, and recalling their own impatience with clingers to office, they announce their joy in the prospect of time for gardening.

On the hypothesis that a limited amount of facilities suitable for such people already exists or can easily be created—off the career ladders and therefore non-competitive—I suggest a special employment agency for retired medical (perhaps also other) research-workers. Applicants for full-time or part-time work would register. It is important that not only the previous line of work be given, but also any private bents which, in a scientifically trained person, might attract a potential employer (I can call to mind an eminent organic chemist who was expert on insect ecology, a bacteriologist clever at scientific advertisement copy-writing, and so on).

The agency should be non-profit-making and academically sponsored. And this leads to a special point in favour of my suggestion. An initial and annual relevant medical examination should be a condition of acceptance of employment through the agency. While primarily intended to avoid awkwardness, this provision would make available an opportunity for gerontological research on the performance of selected intellectuals. Perhaps the N . . . d Foundation would be interested?

For obvious reasons I sign myself merely

"AGED 60".

IS RADIOLOGICAL EXAMINATION OF THE TWISTED ANKLE NECESSARY?

SIR,—I commend Dr. Garfield's iconoclasm (Nov. 26) in examining the desirability of X-raying every injured ankle.

He is right when he says it is often only of medicolegal interest. With extensive casualty experience it is extremely irksome to have to X-ray these injuries, knowing perfectly well that there is no fracture, purely for fear of hearing that dread question in court: "Tell us, doctor, did you X-ray the ankle?" To the lay mind, and to many doctors, an X-ray is a sine qua non of fracture diagnosis and it almost assumes therapeutic importance. Fractures *can* be diagnosed clinically, and in the case of ankle injuries diagnosis rests mainly on the *site* of tenderness—i.e., whether over bone or ligament. It must be stressed that in only about 40% is this sign clinically useful, because where there is bruising or swelling sufficient to obscure bony landmarks X-ray is mandatory.

Dr. Garfield did not discuss treatment, but I should like to expound on a principle which is basic to treatment of a sprained ankle—that the attachments of the ligament must be approximated to allow healing of the torn fibres *in the position of minimum length*. The conventional application of strapping is therefore useless, except as a compressing agent; and this can be better done with crepe bandage.

I have devised a system of strapping which maintains the ligament in its shortest position and, in fact, acts as an artificial external ligament. The steps are as follows:

(1) The patient is instructed to hold the knee bent and the foot in maximum dorsiflexion and eversion during the procedure (as the anterior talofibular ligament is most commonly sprained).

(2) A U-shaped piece of 'Elastoplast' about 15 in. long is applied from the medial malleolus under the instep, and up the leg to adhere in midcalf region. This must be applied under tension, and slightly in front of the axis of the leg (as viewed from the side).

(3) The upper end is fixed with an encircling piece.

(4) The ankle-joint is similarly encircled. This fixes the lower end of the elastoplast and takes up any slack in the "external ligament".

(5) The foot and ankle are enclosed in orthodox figure-of-8 elastoplast in such a way as to maintain the above position—i.e., from the lateral edge of the foot towards the medial malleolus.

If there is considerable swelling it should first be reduced with lotions, elevation, and non-weightbearing exercises.

The support given should be maintained for three weeks, and the elastoplast may have to be changed during that time.

2. Selye, H. The Chemical Prevention of Cardiac Necroses. New York, 1958.

* Since this letter was written we learn that evidence proving that SC-11927 does in fact block the action of aldosterone will appear in the *Proc. Soc. exp. Biol., N.Y.*, in a paper by C. M. Kagawa and E. A. Brown.

A sprained ankle should never be underestimated, as it may leave a considerable morbidity of recurrent pain and instability, and I consider that a strict regime, such as the above, is justified.

Leicester General Hospital. I. G. SCHRAIBMAN.

POST-HERPETIC NEURALGIA

SIR,—I should like to report favourably on the use of ethyl-chloride spraying to treat this condition, as described by Dr. Taverner (Sept. 24). We have now treated three patients and each one has improved.

Male aged 77. Pain behind left ear and down left arm to radial border of forearm. A few scars of vesicles visible in distribution of C5. Duration 16 months. He began to improve after 4 days spraying and was almost free from pain after 8 days. He has had no treatment now for 6 weeks, and is very satisfied.

Male aged 79. Pain around left ribs anteriorly. Two areas of scarring in distribution of T9. Duration 3 months. He began to improve after 3 days, and expressed himself cured after a week. No relapse when seen 2 weeks later.

Female aged 87. Pain around the left ribs anteriorly and posteriorly. Widespread band of scarring in the distribution of T7. Duration 7 months. After a week's spraying the acute paroxysms of pain ceased, but further progress was very slow. Now, after daily spraying for 4 weeks, she reports a 50% improvement. Unlikely to make a full recovery.

Before spraying, these patients had been adequately treated with the usual range of analgesics without relief. The treatment is not expensive, for one bottle usually suffices for two daily treatments at a cost to the hospital pharmacy of under 2*s*.

No advantage was found in using the proprietary product, 'Freon', in place of ethyl chloride.

Barnet General Hospital, Barnet. JOHN BARRETT.

DYSPNŒA DUE TO SUBCLINICAL AMŒBIASIS

SIR,—Disease of the lung or pleura due to infection with *Entamœba histolytica* is not uncommon.

El-Mofti and Moussa,[1] in a study of 900 cases of amœbiasis in Egypt, reported pleuro-pulmonary reactions in 38: cough and chest pain were the chief symptoms and in 15 a pleural effusion developed, while in 6 others a dry pleurisy was present. In 7 patients a lung lesion developed when a liver abscess ruptured through the diaphragm.

Abdel-Hakim and Higazi [2] described 28 cases of amœbiasis with lung changes in which the chief symptoms were pain, hæmoptysis, and cough, although 3 presented with dyspnœa due to a large pleural effusion. In most of these cases some lesion was visible radiologically.

Carri [3] reported 12 cases with allergic symptoms in a series of 120 cases of amœbiasis, 3 of which presented with asthma. In each of these 3 cases permanent improvement in symptoms followed treatment of the amœbic infection, whereas only temporary benefit had been derived from antispasmodic drugs.

The case described below seems to be similar to these three cases.

A 23-year-old man, working in radio assembly, moved to Harlow in September, 1958, and was first seen in January, 1959, complaining of tightness of the chest, associated with attacks of breathlessness and wheezing, for the previous three months. The attacks came on at any time of day, lasted as long as an hour, and were not relieved by the usual antispasmodic drugs. The patient described the attacks as causing him to feel as if he were enclosed in a small space with insufficient air, and stated that his breathing was not noisy as was that of his friends who suffered from asthma. There was no previous history of chest or other illness except that, during his National Service in Egypt in 1954–55 he had had a mild attack of dysentery, which did not necessitate hospital treatment.

His general condition was good, and no abnormal physical signs were found in the lungs or elsewhere. Blood-pressure was 132/70 mm. Hg. Chest X-ray, blood-count, and erythrocyte sedimentation-rate were all normal, multiple-puncture tuberculin test was positive (grade 4), and skin tests, using Bencard reagents, yielded no positive results. In view of the previous history of dysentery, the stools were examined for cysts of *E. histolytica*, and large numbers were present. The patient was admitted to the Hospital for Tropical Diseases under the care of Sir George McRobert, where he received a ten-day course of emetine bismuth iodide and this was followed by three weeks of diodoquin at home. A big improvement in his general condition followed, and the respiratory symptoms rapidly eased. Two months later he was symptom-free and this improvement has been maintained for twelve months.

It is of interest that when the patient's medical card became available it was found that, four weeks after his return to England in 1955, he had consulted his doctor on account of pain in the chest, which recurred during the next three years, and for which his chest had been X-rayed, although no abnormality was ever reported. During the last two years he had complained of breathlessness on several occasions and had had several minor respiratory illnesses described as "flu". On no occasion had his symptoms been sufficiently severe to keep him from work.

This case seemed worth recording as an example of respiratory symptoms due to a latent amœbiasis in a young man after National Service in Egypt. Similar symptoms in a person of the same sex and age, who has served in the Middle East, may have a similar ætiology.

We are grateful to Dr. N. A. F. Young for the examination of the stools, and to Sir George McRobert for permission to publish this account.

IAN HAMILTON
URSULA LUTWYCHE.
Harlow.

ANGOR ANIMI AFTER BENETHAMINE PENICILLIN

SIR,—In view of your annotation about the effects of aqueous procaine penicillin,[1] we should like to describe the following case:

A woman, aged 29, who had had bilateral pulmonary tuberculosis for 5 years, underwent a first-stage thoracoplasty operation on the right, on Aug. 4, 1960, under local anæsthesia with lignocaine. The postoperative period was smooth, except for fever ranging to 104°F from the 3rd day, and slight tachycardia. As well as daily *p*-aminosalicylic acid, isoniazid, and streptomycin, she was also given, on alternate days, injections of 'Benapen Forte', a single-dose vial containing benethamine penicillin 500,000 units, and benzylpenicillin 500,000 units, with buffering and suspending agents.

On Aug. 12—i.e., the 9th day after operation—the patient walked about 30 yards from the ward to the operating-theatre where the sutures were removed with the patient seated. 10 minutes later, when lying down, she was given her fifth intramuscular injection of benapen forte, 1 vial, into the buttock. The nurse and the procedure were the same as for the previous injections. The piston of the syringe was withdrawn as usual, before injecting, and no blood was sucked in. The injection was not painful, but 2 minutes afterwards the patient tried to sit up and complained of feeling giddy. She was helped to lie down, and she shrieked three or four times, and then moaned "I am gone—I am dying—I am not my normal self". When seen by two of us (T. K. and R. P.) within a few seconds, no physical abnormality was found; she was fully conscious and answered questions with slight delay, but she looked dazed, frightened, and confused.

10 minutes later, when seen by P. N. K., she still said that she was going to die, that her husband (100 miles away) should be informed by telegraph about her condition, that her original self had departed from her, that something was radically

1. El-Mofti, A., Moussa, A. H. *Gaz. Kasr. Aini. Clin. Soc., Cairo*, 1951, **17**, 1.
2. Abdel-Hakim, M., Higazi, A. M. *Dis. Chest*. 1958, **34**, 607.
3. Carri, E. L. *Prensa med. arg*. 1948, **35**, 1477.

1. *Lancet*, 1960, i, 1396.

changed in her, &c. She was very frightened but, apart from tachycardia and a slight rise of blood-pressure, there were no abnormal signs. Though her condition did not warrant it, she was given adrenaline 1/1000, 0·5 ml., subcutaneously, followed by promethazine 50 mg. intramuscularly, and sips of hot coffee, which she swallowed without difficulty, taking the cup in her hands.

As there was no change in her mental state about an hour after the attack, a senior consultant (R. K.) was called in; he diagnosed " acute psychic shock ", and she was given chlorpromazine 25 mg. by mouth. 30 minutes later she was taken back to the ward, and immediately she expressed great relief and appeared more relaxed. She was stuporose for a few hours, probably from the effect of chlorpromazine, though she was easily woken to take food. Later in the evening—i.e., about 8 hours after the attack—she expressed regret for her " unusual behaviour". Next morning she had recovered completely.

This case has some features which differ from those of Batchelor et al.[2] and of Björnberg and Selstram [3]:

1. The reaction occurred after benethamine penicillin and benzylpenicillin, and not after procaine penicillin.

2. The patient had not taken her usual breakfast on the morning of the incident, and it was the 3rd day of her menstrual period.

3. Chlorpromazine and/or return to the ward restored her mental equilibrium almost to normal.

In March, 1960, another patient—a man of 45—after the first injection of benapen forte, cried out complaining of intense precordial oppression, a feeling of impending death, severe fright, and intense dyspnœa, but these passed off in a few minutes without any special treatment. As the " reactions " were very alarming no further injection of benapen forte was given to either of these patients.

R. PARTHASARATHI
T. KARUNAKARAN
P. N. KRISHNAN
R. KALAMEGHAM.

Rajaji Sanatorium,
Tiruchirappalli,
Southern India.

TREATMENT OF DRY MOUTH

SIR,—One of the most unpleasant and irritating symptoms of chronic disease must surely be the dry mouth of Sjogren's syndrome and related disorders. We have recently had a patient with scleroderma whose chief discomforts were perpetual dryness of the mouth and great difficulty in masticating food, the result of atrophy of the mucus-secreting cells of the oral mucosa, and probably also of the salivary glands. The physiological stimuli of secretion, such as pilocarpine, were, as might be expected, quite ineffective in stimulating functionally incompetent cells, and continuous sweet sucking left only a nauseous stickiness which was even more unpleasant than the original complaint. It seemed logical to give something which had little taste and, being demulcent, would leave a thin film of mucus-like material in the mouth for a number of hours and which might stimulate to the maximum any remaining active secreting cells.

With these properties in view, pastilles were prepared to the following formula:

Gelatine	20·0
Glycerine	40·0
Sucrose	5·0
Lemon essence (Raynor 159)	0·6
Sodium benzoate	0·2
Citric acid	2·0
Amaranth solution	1·0
Water to	100·0

This is a modified glyco-gelatine, *B.P.C.* 1949. The mass is poured in dry starch moulds and the pastilles dried for twelve hours in warm air.

These pastilles were so successful that it was finally only necessary for the patient to suck one every four hours to ensure a reasonably comfortable mouth and greatly increased enjoyment of her food. She was later discharged with a box of these sweets and writes very appreciatively of their benefit.

They may not have as wide a use as the Brompton lozenge and mixture, but we feel they add strength to the same soothing rather than curative range of treatment.

PETER DYKES
PETER HARRIS
ARTHUR MARSTON.

Queen Elizabeth Hospital,
Edgbaston, Birmingham.

2. Batchelor, R. C. L., Horne, G. O., Rogerson, H. L. *ibid.* 1951, ii, 195.
3. Björnberg, A., Selstram, J. *Acta psychiat., Kbh.* 1960, **35**, 129.

MEDICINE IN THE FACTORY

SIR,—I was interested by your reference (Dec. 10, p. 1288) to the fact that appointed factory doctors (A.F.D.) may be regarded as the principal regular medical force of the factory department. This is true, numerically, but the intention and execution of their statutory duties in respect of young people—which form the major part of their work—is on such a limited and superficial basis that many people have recommended that the examinations should be abolished.

Potentially, if properly used and organised, the A.F.D. service represents a unique opportunity to provide a general industrial service, and a health service for young people at work, comparable to any enjoyed by the more fortunate section who remain at school or go to universities. The Gower report recommended that medical examination should be extended to all young people irrespective of occupation.

Unfortunately, the policy of the Ministry appears to be to fragment the health supervision of young people as much as possible. Their policy is also, apparently, to encourage individuals performing statutory duties to make themselves persona grata to the factory occupier and thus be invited to become the paid adviser to the factory. Surely, an undesirable division of loyalties.

Most A.F.D.s are busy general practitioners and the pressure of work in practice today is already a frequent source of complaint. There is no doubt that many of them would find it difficult to give more time to the examination of young workers unless the present system was reorganised.

You refer to the fact that 97·7% of all factories employ less than 251 workers. The larger factories, on the whole, have the first choice of young workers, and it is those in the smaller factories who often need, and do not get, medical supervision.

According to the annual reports of the Chief Inspector of Factories, the number of examinations on first employment is appreciably greater than that for all subsequent examinations including annual re-examination. The latter figure should be approximately twice as much as for first examinations.

It is the good well-organised firms who report young people for examination, and it is those in the less well-organised firms and those who change jobs most frequently, who most need the type of supervision which A.F.D.s could give if they had the necessary time and training. The A.F.D.s should go into and know more about small factories than almost anyone else. In the course of performing their statutory duties they can also advise on many other problems.

For many years now I have been hoping there might be another experiment of the type I have tried here, and advocated in my report to which you refer. In this connection I am perhaps justified in referring to the opinions expressed by Professor James Mackintosh and King George's Jubilee Trust in the foreword. The latter thought that this type of experiment might form the basis for national development. That was five years ago, and they may of course be wrong.

The pioneer working people realised early in the industrial revolution that to pay special attention to the welfare of young workers was to spearhead improvements for all. This may still be true. We need today a comprehensive approach to medicine. Mind and matter are

indivisible, and there is a growing need to pay more attention to the study and avoidance of mental ill-health which contributed so largely to the 300 million days lost from work through sickness every year. A good place to start might be to pay more attention to the health of young people at work. There is a great need to coordinate as suggested by the Albemarle and Crowther reports and the Dale Committee. Why not experiment?

Farnham Royal, Bucks. M. E. M. HERFORD.

ASTHMA AND THE SEASONS

SIR,—I saw it suggested [1] that because fungus spores and pollens in the atmosphere were a danger to sufferers from hay-fever and asthma, susceptible patients should shut themselves away in midsummer with the doors and windows closed.

A recent survey by Dr. H. Gough-Thomas of children attending the local-authority asthma clinic in Ealing showed that asthmatic children were most often absent from school during December and January when the air contained 2·5–4·0 mg. of SO_3 per day, and only small concentrations of spores and pollens. In May and June when there was 1·75–1·65 mg. of SO_3 per day, but high concentrations of fungus spores and pollens, school attendance was very similar to that in control children. It seems that sufferers from asthma might have to shut themselves away in midwinter too!

Our impression is that there are many causes of asthma and that each case should be treated on its merits.

Hampton Court. MARGARET MCDONALD.

THE CASE FOR ABANDONING THE TRENDELENBURG POSITION

SIR,—We think Swain [2] has done a service in writing his paper and giving it as his opinion that the traditional "head-low" position could today be obsolete, with the continuous advance in new drugs and new techniques. After all Trendelenberg propounded his views seventy years ago.

Your annotation of Nov. 26 finished with the pertinent remark that it remains to be seen whether Swain's suggestion finds favour with gynæcologists, most of whom have been trained to operate with patients in the Trendelenburg position.

McIntyre,[3] in his paper on anæsthesia for hysterectomy, stated that Trendelenburg stressed the fact that forceful respirations hinder the surgeon by causing the intestines to obscure the operative field. Altschule [4] and Case and Stiles [5] have shown that the greater the degree of head-down tilt the more it tends to defeat one of its objects. By favouring the development of anoxia and hypercarbia increased respiratory efforts are caused. The tilt causes œdema of the head and neck, congestion of the cervical veins, and chemosis.

Since 1949, by mutual consent of the three signatories to this letter, Trendelenburg's position has not been used in our group of hospitals. As previously reported by one of us (R. E. L.)[6] all abdominal operations performed by another of us (N. K.) have been performed with the patient horizontal. Over 1300 operations have been carried out. Respiratory or unforeseen cardiovascular complications in the immediate postoperative phase have been exceedingly rare. In spite of routine transfusion with the arm out at just less than 90° there have been no cases of brachial-plexus injury. The patient's heels are always elevated on a cushion (rubber or sand-bag) to prevent pressure on the calves and the incidence of deep vein thrombosis has been negligible. Pulmonary embolism has occurred twice with one death (eighth postoperative day).

Relaxation has been obtained by *d*-tubocurarine chloride.

We do not consider the use of the Trendelenburg position is in the best interests of patients, nor is it necessary for gynæcological surgery. We suggest that all gynæcological surgeons who have been reared in the use of the head-low position should try operating with the table flat.

NORMAN KIMBELL
R. E. LODER
Peterborough. H. S. RICHARDSON.

1. *Times*, Sept. 17, 1960.
2. Swain, J. *Med. J. Aus.* 1960, ii, 536.
3. McIntyre, J. W. R. *Anæsthesia*, 1955, **10**, 359.
4. Altschule, M. D. *Anesthesiology*, 1943, **4**, 385.
5. Case, E. H., Stiles, J. A. *ibid.* 1946, **7**, 29.
6. Loder, R. E. *Anæsthesia*, 1956, **11**, 98.

Parliament

Human Tissue Bill

ON Dec. 8 Mr. ENOCH POWELL, the Minister of Health, introduced this Bill into the Commons. It extends to Scotland but not to Northern Ireland. Its principal purpose is to make clear that parts of a body may lawfully be removed and used for therapeutic purposes, medical education, or research where the deceased had expressed a wish, either in writing or orally in the presence of two witnesses, that his body should be used after death in this way, or where there is no reason to believe that he had expressed any objection or that any relative is opposed to it. The Bill provides that the removal may only be made by a fully registered medical practitioner and that the coroner's consent must be obtained where there is reason to believe that there may be an inquest. In Scotland no authorisation for removal is to be given if the procurator fiscal has objected.

The Bill also confirms that, notwithstanding the provisions of the Anatomy Act, 1832, a postmortem examination to establish or confirm the causes of death, or to investigate the existence or nature of abnormal conditions may lawfully be carried out provided that there are no known objections on the part of the deceased or of his spouse or any surviving relative.

The Bill repeals the Corneal Grafting Act, the provisions of which are included in the more general ones now proposed.

Medicine and the Law

Doctors on Council Housing-estates

WHAT appears to have been an unusually determined attempt by a local authority to control the general-practitioner service on a housing-estate has finally come to nothing, thanks to a decision by the Minister of Housing and Local Government.

It appears that the Hull Corporation had intended to establish doctors in blocks of surgeries on a new housing-estate.[1] When the Minister rejected the plan, Dr. Gareth King had an agreement with the Corporation that he could build a surgery on corporation-owned land at his own expense. Later, however, the Corporation said they were under no obligation to honour the agreement, so Dr. King bought a piece of land near his own home and applied for planning permission to build a surgery on it.

Planning permission was refused, and the Corporation resolved to acquire the land by compulsory purchase. Dr. King appealed to the Minister who, after holding a public inquiry, allowed Dr. King's appeal against the refusal of planning permission and refused to confirm the compulsory purchase order.

Dr. King observed that "the result of the inquiry is a defeat for those local authorities who want to dictate how the Health Service should be run. It defeats any plan to have the medical profession directly under the control of the local authority".

1. *Times*, Dec. 2, 1960.

Obituary

DAVID CARMICHAEL MONRO

C.B., C.B.E., M.B. Edin., F.R.C.S.E.

Major-General D. C. Monro, who died on Dec. 6 at the age of 74, was consulting surgeon to the Middle East Forces during the late war. He was largely responsible for reorganising the medical services to fit the new mobile mechanised war of the desert, and it was thanks to his initiative and resource that the forward operating centres of the 1914-18 war were transformed into the field surgical units of the '40s.

He was born in New Zealand and went to school at Wellington College, but he came to this country to study medicine at the University of Edinburgh where three of his forebears had held the chair of anatomy. The family also had a tradition of military medicine—Donald Monro, F.R.C.P., F.R.S., a great-great grand uncle, was senior physician to the Forces and had served in the Seven Years' War—and David Monro soon after graduating M.B. in 1911 joined the R.A.M.C. He served in France and Belgium during the 1914–18 war, and afterwards he took a Regular commission and served as a specialist in surgery in India and Malta. In 1938 he was appointed assistant professor of military surgery at the Royal Army Medical College and two years later he became professor. During the late war he was consultant surgeon to the Middle East Forces. In 1943 he was a member of the Allied Surgical Mission to Moscow. He retired with the rank of major-general in 1945 but was re-employed as consultant surgeon M.E.L.F. until 1948.

He was appointed C.B.E. in 1942 and C.B. in 1946. He was also a commander of the United States Legion of Merit and was awarded the King Haakon VII Liberty Cross.

Of his work in the Middle East G. A. H. B. writes:

"In every way Jock Monro was a most exhilarating personality, and had an intimate knowledge of the surgical work and of the personalities of all connected with it. He did a great deal towards the promotion of the wonderful cooperation in M.E.F. He was such a jovial and lovable personality that everyone found it a pleasure to work with him. The war in the desert involved huge distances between forward troops and casualty-clearing stations and Jock developed the idea of putting surgical units very far in advance of what had previously been thought possible. In 1941 he arranged for two such units to be with the field ambulances and thus saved a great deal of time in operating on seriously wounded men, who might have died on the lines of evacuation. Together with Sir John Boyd he arranged the close association of field surgical units with field transfusion units and thus it was possible to transfuse to wounded men before operating. This development of forward surgery has undoubtedly led to the saving of a great many lives, especially in the case of abdominal wounds where every movement before operation added so much to the risk."

J. S. K. B., who first met Major-General Monro in 1923, when they were on the same senior officers' course at Millbank, relates:

"I can still see Jock as he was then—slim, erect, bursting with energy and full of joie-de-vivre. He was the friendliest of souls, as much at home with those of exalted rank (whom in those days we regarded as somewhat formidable) as with the orderlies who attended to our needs in the laboratories. Wherever he might be, his infectious laugh was never long silent. He had an endless and ever-changing fund of stories, which he enjoyed as much as his listeners.

"As consultant surgeon to the Middle East Forces in Cairo he was in his element. His duties called not only for a high degree of technical knowledge of the special kind of surgery required in the unusual conditions which obtained there; they called also for great administrative ability and for no small measure of tact, as personalities were many and diverse, yet all had within limits to conform to a common plan. It was my privilege to have somewhat similar duties in another subject, and it was very clear to me that Jock's commonsense appreciation of the special needs of desert warfare, and the modifications he introduced, and the encouragement which he gave to all, played a major part in the evolution of an enthusiastic surgical service to which the wounded soldier owed a very great debt. And wherever he went there was still the same apposite story and hearty laugh which did everyone a world of good.

"After retirement from the active list some 15 years ago, we continued to meet at regular intervals. Inevitably, advancing years took their toll on bodily activity, but Jock never grumbled. His spirit never changed, and he refused to make an invalid of himself. When he could no longer play golf—and what a sorrow this must have been—he turned out regularly to Corps matches and took his stance at some convenient spot where he greeted his passing friends with the same gay laugh we have known for so many years, and which we will never forget."

Major-General Monro married Kathleen Noone in 1942 and they have an adopted daughter.

Sir HAROLD BOLDERO

T. C. H. writes:

"Harold Boldero combined the most sincere kindness and thought for the individual with great wisdom and regard for general principles. If it is true that a sense of proportion is the greatest factor that contributes to wisdom, Harold Boldero surely showed this to the utmost.

"His long experience and shrewd judgment were flavoured with a wonderful sense of humour, and many owe him a deep debt of gratitude for his advice and help: advice for which they felt they could always turn, however busy he might be. He had a gift of making troubles seem light and would often find an approach to a problem which by its directness and apparent simplicity made its solution easy. Boldero had a tolerance and understanding which brought him many true friendships amongst his colleagues of all ages, and his humour and patience made him able to enjoy situations which others found galling or fatiguing.

"He had little regard for who got the credit provided he could feel that a job was well done—and the thought and skill which he gave to preparing an agenda or a draft made the burden light for others. His letters were like himself—clear, amusing, always to the point, and in a style that was especially his own.

"He was a man whose interests were wide and varied and his presence at a dinner party would ensure its success. His witty and sometimes apparently cynical comments on the foibles of human nature and the oddities of his times gave no indication of his great sympathy with his fellow men: perhaps particularly with the young. He showed none of that weakness of older men—a too great preoccupation with the past—but was ready and anxious to move forward to new ideas and new methods: he had a constructive attitude to suggestions where others might criticise without offering useful alternatives. He will be deeply missed not only for the help, but even more for the friendship and pleasure which his life gave to so many."

Appointments

CARR, DOROTHY M., M.B. N.U.I., F.F.A.R.C.S.: honorary anæsthetist, Italian Hospital, London.

EARL, C. J., M.D. Lond., M.R.C.P.: consultant physician, neurological department, London Hospital.

FORDYCE, F. W., M.B. Durh.: school M.O., Northumberland.

HILTON, R. W., M.B., B.SC. Aberd.: assistant M.O. and school M.O., Bradford.

MCDONALD, E. L., M.D. Cantab., M.R.C.P.: consultant physician, cardiac department, London Hospital.

MCNAIR, T. J., M.B. Edin., F.R.C.S.: consultant in general surgery, Edinburgh teaching hospitals.

MORTIMER, DOUGLAS, M.B. Aberd.: assistant M.O.H. and school M.O., Wakefield.

ROSS, J. A., M.B.E., M.D. Edin., F.R.C.S.E.: consultant in general surgery, Edinburgh teaching hospitals.

Liverpool Regional Hospital Board:

GRAY, T. D. H., M.B. Lpool, F.R.C.S.: part-time consultant ophthalmologist, Broadgreen, Alder Hey Children's, and Birkenhead General Hospitals.

HONEY, G. E., D.M. Oxon., M.R.C.P.: consultant physician, Walton Hospital.

JONES, E. S., M.B., PH.D. Lpool, M.R.C.P., D.T.M. & H.: consultant physician, St. Helens and district H.M.C.

Notes and News

THOMAS LINACRE

THE 500th anniversary of the birth of Thomas Linacre is being celebrated by the Royal College of Physicians of London this year, and on Dec. 8 the Linacre oration was given by Sir George Clark, the historian.

Although the college was in form a royal foundation, Linacre, he said, has always been rightly regarded as its real founder. He was also its president from the beginning in 1518 until his death in 1524, and he was its first benefactor. His wealth was acquired at least partly from a successful professional career by the end of which he was the head of the medical household of King Henry VIII. Among his contemporaries, however, he was chiefly famous as the first Englishman who made a substantial contribution to the revival of Greek learning and as the first Englishman with a European reputation as a classical scholar. These two aspects of his achievement may seem now to have little relation to one another, but in fact they formed a well-knit unity.

He was born in 1460 or 1461 (the exact date is unknown). He was *Cantuariensis*, but this may mean that he was born not in the city but in the diocese of Canterbury. Modern research has demolished the accounts of his parentage and early years which were formerly accepted, and the first well-attested fact of his life is that he was elected a fellow of All Souls College, Oxford, in 1484. Whether he began to study Greek or medicine in Oxford is unknown, but there were opportunities in both fields. One of his colleagues at All Souls, sixteen years his senior, lived to be a charter-fellow of the College of Physicians, and another, his junior, was the first to be admitted after election.

In 1487 Linacre went to Italy, and it was not until 1499 that he returned to England to settle down. During these years he worked in the inner circles of the revival of learning. In Florence, at the court of Lorenzo the Magnificent, he learned Greek from the best masters. In Rome he served for a year as warden of the English hospice. In Padua he took his degree as doctor of medicine. In Venice he lived for several years in the house of Aldus Manutius, the greatest of all printers of classical texts. He devoted himself especially to the manuscripts of Greek scientific and medical works. When he left Italy he was a recognised authority on these, and he had completed the first of his works to be published, a Latin translation of the little treatise of Proclus on the terrestrial globe.

Back in England he was one of the leaders in the wonderful circle—Grocyn, Latimer, Colet, Erasmus, Thomas More, and their friends—who began the continuous history of Greek scholarship and teaching here. His friends reproached him with being slow to publish; but, in spite of the other calls on his time, his achievement in that line was very considerable. He lectured on the scientific work of Aristotle, but his published work dealt mainly with Galen, who was for that time the most important of the Greek medical writers. Galen's works were published in Greek in five large folio volumes by the successor of Aldus in 1525, but before that there was a period of about thirty years in which the most fruitful method of recovering Galen's medical science was to translate from the manuscripts into Latin. Linacre, with a higher standard of scholarship than most of the translators, dealt in this way with two of Galen's major works, and his translations ranked as standard works, often reprinted in various Continental cities. Besides several shorter pieces of Galen, and a school Latin grammar, he provided other scholars with a valuable tool, a full grammar of the Latin language. This too was long and widely celebrated.

Except for one visit to Paris as physician in the suite of King Henry's sister Mary, Queen of France, Linacre spent the years of his prosperity at his house, the Stone House in Knightrider Street, close to St. Paul's Cathedral. London in his day was exceptional among the greater cities of Europe in having no organised body of physicians. This does not mean that its medical doctors were an undisciplined rabble: they were very few in number and they were bound together by a great ethical and educational tradition. But there was a need for system in the granting of licences to practise and for direction in the repressing of irregular practitioners. These were the ends which the College of Physicians furthered. It was not intended to be a teaching body: for that purpose Linacre conveyed landed estates which he had bought in Kent to trustees who were to establish medical lectureships in Oxford and Cambridge. So far as the London college followed any existing models, it seems to have adopted some features of English guilds and companies, and some of Florentine, Venetian, and other Continental medical corporations.

Many writers, Sir George said, have represented Linacre as a forerunner of the scientific spirit or even of the Protestant Reformation. We know too little of his mind to guess what he thought of the new religious movements which afterwards divided the circle of his friends. During his lifetime they were scarcely heard of in England. He was an ecclesiastic; he held many Church preferments, and he was ordained priest as late as 1520, when he was about 60. The many-sided Italian renaissance, in which he played more than a minor part, had an element of science in it, but much else too. We do not know whether Linacre ever heard of the anatomical investigations of Leonardo da Vinci; but we do know that he was a fellow-pupil of Pope Leo X. So far as his mind and action are known to us, it seems that he used his learning and his wealth in the ways that the ideals of his early manhood dictated.

THE KING'S FUND

THE Duke of GLOUCESTER, presiding at a meeting of the general council of King Edward's Hospital Fund for London on Dec. 8, said that the Fund was constantly looking for new ways in which to help patients by improving conditions in hospitals. To this end the reports provided by the official visitors were most valuable, and, as examples, he cited the survey on noise control, of which some 14,000 copies had been circulated since 1957, and the recent manual on hospital visiting,[1] for which the demand was so great that a second edition of 5000 had to be ordered within ten days of publication. The preparations for courses in work study at the Hospital Administrative Staff College were now complete, and it was hoped gradually to train work-study officers for all the hospital groups which needed them. A three-month course for administrators from the Commonwealth was to begin in April.

Lord MCCORQUODALE, the chairman, said that there had been exceptionally heavy non-recurrent expenditure owing partly to the purchase of a site in Holland Park on which a new and larger staff college for ward sisters was to be built, and the purchase and adaptation of a house which would enable the Hospital Administrative Staff College to take 25 additional students.

Two new committees were to be set up—a colleges committee to deal with matters of policy regarding the three staff colleges and school of catering, and a hospital development committee to consider projects submitted to the Fund, such as a centre for information on experiments proceeding throughout the hospital service. It seemed likely, in Lord McCorquodale's view, that in the next decade it would become less necessary to make grants for hospitals' needs and that more attention would be given to inquiry and experiment, and to the pioneering of new ideas and new schemes for the benefit of hospitals.

HALF-WAY HOSTEL

EARLIER this year Dr. D. H. Clark and Mr. L. W. Cooper described the beginnings of an interesting Cambridge experiment in community medicine.[2] Winston House, with the triple support of the Cambridgeshire Mental Welfare Association and County Council and the S.O.S. Society, was opened in October, 1958, as a hostel for patients who had lately left a mental hospital and were ready to try once more to earn their own living. During its first year, rather surprisingly, it was never completely full, but the report of the second year suggests that this was chiefly because the right people had not yet

1. See *Lancet*, Dec. 10, 1960, p. 1311.
2. *ibid.* 1960, i, 588.

learned of its existence. For the whole of the second year it has been nearly full, and indeed in the latter half there has always been a waiting-list. The average daily number of residents was 21. There were 57 admissions during the year (compared with 36 in the first year) and 50 departures (22 in the first year).

The 50 departures were made by 46 people, for sometimes residents return after an unsteady independent start. 11 departures were regarded as thoroughly satisfactory, and 15 as fairly satisfactory. Of the others, 7 residents returned to a mental hospital. Only 4 residents (2 alcoholics, 1 aggressive psychopath, 1 inadequate psychopath) had to be asked to leave because their behaviour was disturbing the hostel. Taking the results of the first two years together, 41 people—or about two-thirds of those admitted—have made a satisfactory transition to the outside world.

During the year the age-limits for admission have been widened, and residents now range from sixteen-year-olds to those in their sixties. As the hostel has become more widely known, more patients have been drawn from other hospitals than Fulbourn Hospital and from more distant parts than Cambridgeshire. Last year Dr. Clark suggested that admissions of this kind would be welcome, for they would bring new interests to the hostel; and this has proved to be so. Mr. Cooper, the warden, has also welcomed this year as residents some professional men and women. "Graduates, military officers, and public schoolboys have mixed and learned together with labourers, hospital ward maids, domestics, shop and factory workers. All have a common meeting ground of recent mental illness and each appreciates the others' need of sympathy, friendship, encouragement, and understanding in a community life." All the residents of Winston House are selected because they are thought to be capable of achieving independence; but a few have failed, and Dr. Clark admits that during the year he has become more and more aware of the need for hostels for people who are never likely to be able to live on their own.

ANTIBIOTIC OR SULPHONAMIDE?

THE increasing use of sulphonamides as an alternative to antibiotics is discussed by Bergfors [1] in a sort of sulphonamide-antibiotic A.B.C. designed primarily to help the general practitioner. Since the early days of the sulphonamides there has been a considerable reduction of side-effects and complications without loss or efficacy: thus a complication-rate of 0·4% for one of the newer ones can be contrasted with a complication-rate of 18·6% for one of the older. There has also been a change in the spacing of the doses, from one every 4 hours to one or two every 24. Bacterial resistance seems to develop more slowly to sulphonamides than to antibiotics, and many of the bacteria primarily resistant to antibiotics are sensitive to sulphonamides. As regards expense, one of Bergfors' tables shows the cost of a 6-day course of treatment under policlinic conditions for a 3-year-old child who has the choice of ten sulphonamides and nine antibiotics. The cost of the sulphonamides ranges from 4·20 to 11·95 Swedish crowns, while the cost of the antibiotics ranges from 7·70 to 40·30. But Bergfors notes that in Sweden the sale of one of the cheapest sulphonamides is quite modest, whereas a comparatively expensive one accounts for more than half of all sales for the sulphonamide group.

IMPENDING SURVEY OF MENTAL HEALTH SERVICES

ADMINISTRATIVE changes in psychiatry have been considerable, and the Mental Health Act of 1959 will alter the scene even more. Systematic reporting and evaluation of these changes have been slow to get under way; and it is excellent news that P.E.P., with the help of the Nuffield Provincial Hospitals Trust, have started a three-year survey of the mental health services with particular emphasis on community care. As a P.E.P. pamphlet [2] points out:

"It is unusual . . . for new legislation to be preceded or accompanied by systematic investigation, as contrasted with the more discursive type of enquiry characteristic of Royal Commissions, which might provide a factual basis for policy-making and planning."

It seems that this survey will cover the structure and operation of services in selected districts together with the social and personal consequences for patients and families, and make a sort of time and motion study of the various staff members involved. The role of the family doctor, and attitudes of profession and public towards mental illness, are included; and there will be a glance at the services for the mentally subnormal. No controlled experimental approach to assess the effectiveness of new methods seems to be envisaged. The P.E.P. pamphlet also summarises historical trends in psychiatric care, gives short accounts of local-authority services (existing and proposed), and describes an interesting follow-up of discharged patients in Scotland. P.E.P. expects to collaborate with other researchers; and, if the project is to be carried through at all, will clearly need much cooperation from the many who are involved. We hope that this will be given freely.

FILMS ON HOSPITAL INFECTION

Two recent films are concerned with the spread of resistant strains of staphylococci in hospitals and recommend methods of reducing the risk of cross-infection.

Hospital Sepsis: a Communicable Disease [1] (16 mm., sound, colour, 29 minutes, U.S.A., 1959) illustrates the case of a patient admitted to the Peter Bent Brigham Hospital, Boston, with a specifically identifiable staphylococcal infection. Although she was nursed in a specially prepared room, the organism was later identified throughout the hospital. The film examines the concentration of organisms on and around the patient following various nursing procedures and the routes by which the infection left the room. Among the reservoirs and multipliers considered are the floor-mops, bed-linen, mattresses, drinking-water, soap, and the ventilation plant; and suggestions are made for dealing with these and with other infected material leaving the room.

This excellent film presents the problem vividly and gives sound advice. It could usefully be shown to most of those who work in hospitals, including ward orderlies, engineers, and administrators.

Hospital Cross-Infection: Dressing Techniques in Wards [2] (16 mm., sound, colour, 26 minutes, Great Britain, 1960), which was made with the cooperation of the Sterilising Research Unit at Little Bromwich General Hospital, Birmingham, discusses the spread of organisms from an infected patient or member of the ward staff to the reservoir and the target, and shows how weaknesses in normal hospital routine and procedures may promote this spread. A separate room on a ward, built on the principle of an operating-theatre, in which all dressings are carried out is suggested, and the advantages of a central sterile supply department and of the use of disposable materials are mentioned. Finally wound-dressing techniques, first for use by a single nurse and then by two nurses, are demonstrated.

Although a good film, this is not as well organised as the American one, but the recommended nursing procedures make it valuable for use by sister-tutors.

University of Dublin

On Dec. 8 the following degrees were conferred:

M.D.—F. L. Willington.

M.B., B.Ch., B.A.O.—A. D. S. K. Allen, E. F. Brown, Judith A. Bryan, D. D. Duncan, A. N. Dunn, J. G. G. Eglinton, Celia F. Twisleton-Wykeham Fiennes, J. J. Gorman, J. D. McCarter, Sheila P. McGuinness, Bohdan M. Meeson, Denise R. Millin, R. A. H. Mooney, J. R. Press, P. J. W. M. Sang, R. E. Snow, Margot V. Thomas, Deirdre M. Verling.

L.M., L.Ch., L.A.O.—Archibald Redman.

British Association of Otolaryngologists

The following officers have been elected:

President, Prof. V. F. Lambert; immediate past president, Mr. C. Gill-Carey; vice-president, Mr. M. L. Formby; hon. treasurer, Mr. J. C. Hogg; hon. secretary, Mr. G. H. Bateman.

1. Bergfors, P. G. *Svenska Läkartidn.* Oct. 14, 1960.
2. Community Mental Health Services. *Planning*, 1960, **26**, no. 447. Published by Political and Economic Planning, 16, Queen Anne's Gate, London, S.W.1. Pp. 15. *2s. 6d.*

1. Hospital Sepsis: a Communicable Disease (film and booklet); available without charge from Johnson & Johnson, Ltd., 260, Bath Road, Slough, Bucks.
2. Hospital Cross-Infection: Dressing Techniques in Wards (film and booklet); available without charge from Smith & Nephew-Southalls Ltd., 5/7, Singer Street, London, E.C.2.

Royal College of Surgeons of England

At a meeting of the council on Dec. 8, with Sir Arthur Porritt, the president, in the chair, Lord Kindersley was admitted to the court of patrons. Prof. Digby Chamberlain was appointed Bradshaw lecturer for 1961, and Mr. G. T. Hankey was awarded the John Tomes prize for 1957–59.

Diplomas of fellowship were granted to the following:

C. M. Ruben, A. E. Steel, J. H. F. Batstone, S. K. Bosher, D. C. Gardner, R. A. James, H. J. S. Waldeck, J. G. Jeffreys, W. M. Mee, E. E. Denman, G. C. W. Baker, B. G. Andrews, G. R. E. Roberts, Molly E. Wakely, A. W. F. Lettin, Theodore Chukwuemeka Ezeokpue Mbanefo, Ajeet-Bans Lall Gulati, Christopher Wastell, Alexander Cort, G. N. McG. Orr, Samuel Gopal Ramaiya, A. J. de Bruin, P. D. Livingstone, Birinchi Prasad Samanta, Hyman Kramer, D. J. Adams, Arthur Bates, I. F. Maclaren, R. K. McRae, Harish Chandra Puri, Dhun Dinshaw Sumariwalla, P. J. Chesterman, Ahmed Abdulla Kazim, J. P. Masterton, C. R. Fenton, B. G. Haggart, D. W. M. Haw, Hon Fah Ho, J. G. Mander, Thamotherampillai Nadarajah Shanmugalingam, Trevor Sussman, J. W. P. Bradley, G. G. Dinning, Earl Ming-Teh Lu, G. W. Crock, D. L. Crosby, D. D. Foster, R. W. Goonewardene, A. H. Grabham, J. M. S. Hague, M. B. Heywood-Waddington, C. T. Howe, J. A. Hunt, E. O'G. Kirwan, Adi Eruch Mody, A. E. J. Mullins, Sannapareddi Sreenivasulu Reddy, C. J. C. Renton, I. G. Schraibman, Letchumanan Sivaraman, M. J. Betty, G. J. Bougher, L. J. Caust, B. C. Cohney, G. A. G. Decker, K. M. Dickinson, J. R. P. Gibbons, D. U. Hay, D. W. Hossack, J. B. Laine, D. J. McAuliffe, R. A. Owen, Ballambetto Yogish Pai, Henry Poirier, D. M. Ritchie, G. R. Thoms, D. L. Annetts, Baldev Raj Bahl, P. M. Binns, F. J. Collins, S. R. Duke, Hassanein Mohamed Hassanein El-Sherif, W. M. P. Fennell, D. C. Glenn, M. C. Green, W. G. Harris, P. McR. Higgins, C. N. Hudson, J. N. Kille, Richard Lenaghan, C. J. H. Logan, Gearoid Lynch, Brian McKibbin, Prithvinath Dinanath Madhok, H. R. Magee, P. M. Meffan, G. J. Ormandy, W. H. Reid, R. L. Rothwell-Jackson, C. E. Rowell, Leo Rozner, P. M. Scott, Bhanu Ratilal Shah, H. L. McI. Smith, A. P. Wyatt, Hameed Ud-Deen Ahmed, C. W. P. Canagaretna, Jagdish Kumar Chaudhry, Eugene Poh Hwye Chu, Sohan Lal Johari, K. F. King, Franklin Wang-Pong Li, W. S. Pease, N. M. A. Rogers, J. A. Russell, R. T. Southwood, Jamsheed Cooverji Taraporvala, Marthanda Varma Sankaran Valiathan, P. J. Venter, Ivo Smith, M. F. Stranc, Vasant Charuchandra Talwalker.

Royal Faculty of Physicians and Surgeons

At a meeting of the faculty on Dec. 5, with Dr. J. H. Wright, the president, in the chair, the following were admitted to the fellowship *qua* physician:

John Ballantine, Shantakumar Dnyaneshwar Bhandarkar, Hugh Conway, Bruce Cruickshank, Jayanta Kumar Dutta, A. T. Elder, Arvind Sadashiv Godbole, Mohammed Shamsul Haque, Cheng Hing Ip, Tit Shing Ip, A. I. Macdougall, Kantibhai Maganbhai Patel.

Royal College of Physicians of Edinburgh

The following officers have been elected for the coming year:

President, Dr. J. D. S. Cameron; vice-president, Dr. I. G. W. Hill; members of council, Dr. J. G. M. Hamilton, Dr. Thomas Anderson, Dr. A. W. Wright, Dr. H. J. S. Matthew, Dr. C. W. Clayson; treasurer, Dr. J. A. Bruce; secretary, Dr. R. F. Robertson; hon. librarian, Dr. W. A. Alexander; registrar, Dr. William Macleod.

Welsh National School of Medicine

Dr. J. G. Leopold has been appointed senior lecturer in pathology.

Hunterian Society

The dinner meeting of this society on Monday, Dec. 19, at the Talbot Restaurant, London Wall, London, E.C.2, will be followed at 8.30 P.M. by a discussion on the Mechanism of Conversion to Brainwashing, which will be opened by Dr. W. W. Sargant.

European Academy of Allergy

A meeting of this academy will be held on April 28 and 29 in Berlin. The main subjects chosen for discussion are differential diagnosis of bronchial asthma and destructive emphysema of the lung, and neurodermatitis and contact eczema. The speakers will include Prof. Jethro Gough. Further particulars may be had from Dr. H. Michel, Berlin-Charlottenburg 9, Krankenanstalten Westend.

Sully Hospital

On Monday, Dec. 19, Sir Clement Price Thomas, the president of the Welsh National School of Medicine, is opening the new cardiac laboratory in this hospital.

This department has been equipped by the Welsh Regional Hospital Board with Philips' cineradiography apparatus including an 11 in. and 5 in. image intensifier. A Philips' closed-circuit television system is used for cardiac catheterisation with the 5 in. image intensifier. Other equipment in the laboratory includes a Sanborn 6-channel direct-writing recorder with pressure transducers, a Norman N.E.P. Dye curve assembly, and equipment for photometric blood-gas analysis and radioisotope measurements.

Leeds Neurological Sciences Colloquium

A meeting of the colloquium will be held on Tuesday, Dec. 20, at 5.15 P.M., at the General Infirmary at Leeds, when Sir Russell Brain will speak on the Cerebral Basis of Mind.

Army Appointments

Major-General W. R. M. Drew has been appointed commandant and director of studies to the Royal Army Medical College in succession to Major-General W. D. Hughes. Brigadier W. H. Hargreaves has succeeded Major-General Drew as director of medicine and consulting physician to the Army.

Prof. T. C. Gray has been appointed honorary consultant in anæstnetics to the Army, and Dr. R. Miles Gibson honorary consultant in neurosurgery to Catterick Military Hospital.

Medical Women's Federation

Christine Murrell fellowship (£150).—The Federation invites applications for this award from women doctors. Full details will be found in our advertisement columns.

Tumour Biology

A meeting on this subject, organised by the Cancer Research Commission of the International Union against Cancer, is to be held in Warsaw, Poland, from May 22 to 27. Further particulars may be had from Prof. O. Mühlbock, chairman of the Cancer Research Commission, Sarphatistraat 108, Amsterdam, Holland.

Hostel for Deaf Children

King Edward's Hospital Fund for London has made a grant of £20,000 to buy and adapt 6, Castlebar Hill, Ealing for use as a hostel for deaf children who are attending the audiology unit of the Royal National Throat, Nose, and Ear Hospital.

The new hostel (which adjoins the existing hostel for mothers and very young deaf children) will take 20 children of varying ages and will enable longer and more intensive periods of training to be given. Mothers, and occasionally fathers, will be able to stay at the hostel from time to time.

Opportunities in Hospital Administration

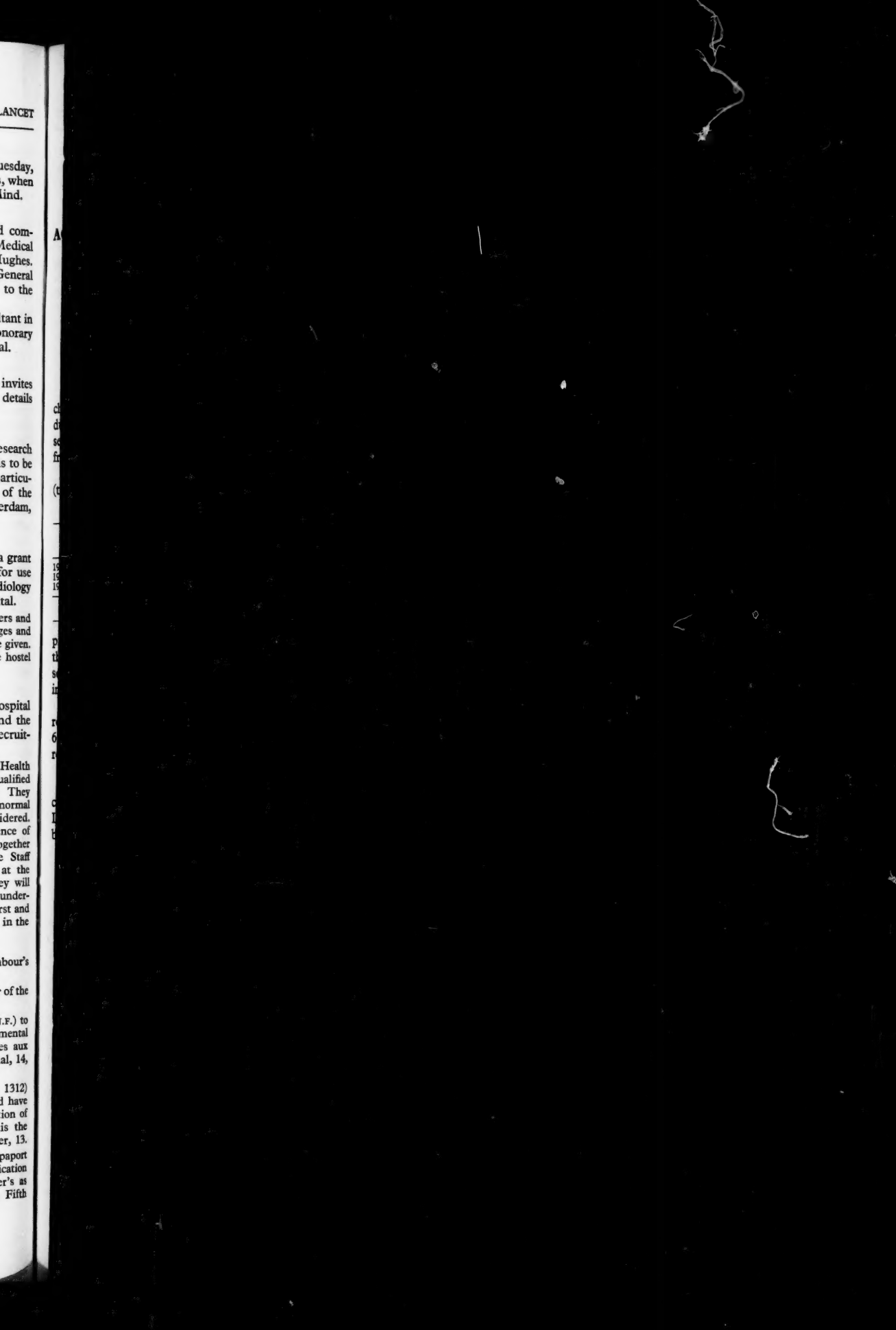
Applications for training posts for prospective hospital administrators are invited by the Minister of Health and the Secretary of State for Scotland under the National Recruitment and Training Scheme begun in 1956.

The posts are open both to young officers in the National Health Service and to university graduates and professionally qualified people who wish to make hospital administration their career. They are tenable for three years beginning in October, 1961. The normal age-limit is 30, but candidates up to the age of 35 may be considered. The student administrators will be given practical experience of hospital administration with different hospital authorities, together with courses of instruction at the Hospital Administrative Staff College of King Edward's Hospital Fund for London or at the University of Manchester. Their fees will be paid and they will receive a salary beginning at £605. At present 42 candidates are undergoing training, 4 of them women. With one exception, the first and second groups of trainees have found permanent employment in the hospital service.

Sir Harry Platt has been appointed the Ministry of Labour's regional medical adviser for the north-west.

Mr. R. B. Zachary has been elected a corresponding member of the Czechoslovak Medical Society, J. E. Purkinje.

The French review *Agressologie* is offering a prize (2000 N.F.) to workers under 35 years of age for an essay on a clinical or experimental subject "de physio-biologie ou de pharmacologie appliquées aux effets de l'agression". Particulars may be had from the journal, 14, rue Drouot, Paris IX.

CORRIGENDA: *New Proceedings*.—In this note last week (p. 1312) "chemical" appeared at two points where "clinical" should have been printed. The *Proceedings* are published by the Association of Clinical Biochemists; and the address of the hon. editor is the department of clinical pathology, Royal Infirmary, Manchester, 13.

Pulmonary Emphysema.—In this article by Dr. Israel Rappaport and Dr. Edgar Mayer (Dec. 3, p. 1217), Dr. Rappaport's qualification should have been shown as M.D. Budapest, and Dr. Mayer's as M.D. Columbia, N.Y. The authors' present address is: 850, Fifth Avenue, New York 21, N.Y.